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=> fil hcaplus

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FILE COVERS 1967 - 23 Jun 1999  VOL 130 ISS 26
FILE LAST UPDATED: 23 Jun 1999  (19990623/ED)

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 all substance data from the REGISTRY file.  Enter HELP FIRST for
 more information.


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=> d stat que l5 1-4

'1-4' IS NOT VALID HERE

=> d stat que l5

L1           31 SEA FILE=REGISTRY ABB=ON  PLU=ON  INTERLEUKIN 18?/CN
L2          262 SEA FILE=REGISTRY ABB=ON  PLU=ON  OSTEOCLAST/BI
L3          221 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L1 OR (INTERLEUKIN OR
                IL)(W)18 OR IGIF? OR INTERFERON(W)GAMMA(W)INDUCING(W)FACTOR
L4         4126 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L2 OR OSTEOCLAST?
L5            4 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L3 AND L4

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=>

=> d ibib abs hitrn l5 1-4


L5   ANSWER 1 OF 4  HCAPLUS  COPYRIGHT 1999 ACS
ACCESSION NUMBER:         1998:603139  HCAPLUS
DOCUMENT NUMBER:          129:215727
TITLE:                    Osteoclastigenesis-inhibitory agent
                          comprising interleukin-18
INVENTOR(S):              Gillespie, Matthew Todd; Horwood, Nicole Joy; Udagawa,
                          Nobuyuki; Kurimoto, Masashi
PATENT ASSIGNEE(S):       Kabushiki Kaisha Hayashibara Seibutsu Kagaku Kenkyujo,
                          Japan
SOURCE:                   Eur. Pat. Appl., 56 pp.
                          CODEN: EPXXDW
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.       KIND  DATE           APPLICATION NO.  DATE
     ---------------  ----  --------       ---------------  --------
```

EP 861663 A2 19980902 EP 98-301352 19980224
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO
JP 10236974 A2 19980908 JP 97-55468 19970225
PRIORITY APPLN. INFO.: JP 97-55468 19970225

AB An **osteoclastigenesis**-inhibitory agent which comprises an **interleukin-18** and/or its functional equiv. is disclosed. The agent can be arbitrarily used as an ingredient for cell culture and agents for regulating bone resorption and for **osteoclast**-related diseases, directed to treat and/or prevent hypercalcemia, **osteoclastoma**, osteoporosis, etc.

IT **189304-55-0, Interleukin 18** (human)
208197-35-7, Interleukin 18 (mouse)
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(amino acid sequence; **osteoclastigenesis**-inhibitory agent comprising **interleukin-18**)

L5 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1998:566420 HCAPLUS
DOCUMENT NUMBER: 129:314628
TITLE: Interleukins in the control of **osteoclast** differentiation
AUTHOR(S): Martin, T. J.; Romas, E.; Gillespie, M. T.
CORPORATE SOURCE: St. Vincent's Institute of Medical Research, Fitzroy, Victoria, 3065, Australia
SOURCE: Crit. Rev. Eukaryotic Gene Expression (1998), 8(2), 107-123
CODEN: CRGEEJ; ISSN: 1045-4403
PUBLISHER: Begell House, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with approx. 140 refs. To maintain homeostasis of bone, the prodn. of osteoblasts and **osteoclasts** is tightly regulated. At the local level, hormones and cytokines control formation of **osteoclasts** from hemopoietic precursors by acting upon osteoblastic-stromal cells and in some cases also upon cells of the immune system. Osteoblasts regulate **osteoclast** formation by providing phys. support and cytokines such as M-CSF and IL-11, which promote **osteoclast** differentiation. Osteoblasts are also a source of **IL-18**, which limits **osteoclast** formation. The requirement of contact between osteoblasts and hemopoietic cells for successful **osteoclast** formation led to a concept of a membrane-anchored stromal cell mol. that programs **osteoclast** differentiation. This mechanism has been highlighted by the discovery of osteoprotegerin (OPG), a sol. tumor necrosis factor (TNF) family member that inhibits **osteoclast** formation. The ligand for OPG is a novel transmembrane TNF receptor superfamily member, the **osteoclast** differentiating factor (ODF).

L5 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1998:84241 HCAPLUS
DOCUMENT NUMBER: 128:191446
TITLE: **Interleukin 18** inhibits **osteoclast** formation via T cell production of granulocyte macrophage colony-stimulating factor
AUTHOR(S): Horwood, Nicole J.; Udagawa, Nobuyuki; Elliott, Jan; Grail, Dianne; Okamura, Haruki; Kurimoto, Masashi; Dunn, Ashley R.; Martin, T. John; Gillespie, Matthew T.
CORPORATE SOURCE: St. Vincent's Institute of Medical Research and The University of Melbourne, Department of Medicine, St. Vincent's Hospital, Fitzroy, 3065, Australia
SOURCE: J. Clin. Invest. (1998), 101(3), 595-603
CODEN: JCINAO; ISSN: 0021-9738

PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **IL-18** inhibits **osteoclast** (OCL) formation in vitro independent of IFN-.gamma. prodn., and this was abolished by the addn. of neutralizing antibodies to GM-CSF. The authors now establish that **IL-18** was unable to inhibit OCL formation in cocultures using GM-CSF-deficient mice (GM-CSF -/-). Reciprocal cocultures using either wild-type osteoblasts with GM-CSF -/- spleen cells or GM-CSF -/- osteoblasts with wild-type spleen cells were examd. Wild-type spleen cells were required to elicit a response to **IL-18** indicating that cells of splenic origin were the **IL-18** target. As T cells comprise a large proportion of the spleen cell population, the role of T cells in **osteoclastogenesis** was examd. Total T cells were removed and repleted in various combinations. Addn. of wild-type T cells to a GM-CSF -/- coculture restored **IL-18** inhibition of **osteoclastogenesis**. Major subsets of T cells, CD4+ and CD8+, were also individually depleted. Addn. of either CD4+ or CD8+ wild-type T cells restored **IL-18** action in a GM-CSF -/- background, while **IL-18** was ineffective when either CD4+ or CD8+ GM-CSF -/- T cells were added to a wild-type coculture. These results highlight the involvement of T cells in **IL-18**-induced OCL inhibition and provide evidence for a new OCL inhibitory pathway whereby **IL-18** inhibits OCL formation due to action upon T cells promoting the release of GM-CSF, which in turn acts upon OCL precursors.

L5 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1997:192313 HCAPLUS
DOCUMENT NUMBER: 126:262973
TITLE: **Interleukin-18 (interferon -.gamma.-inducing factor**) is produced by osteoblasts and acts via granulocyte/macrophage colony-stimulating factor and not via interferon-.gamma. to inhibit **osteoclast** formation
AUTHOR(S): Udagawa, Nobuyuki; Horwood, Nicole J.; Elliott, Jan; Mackay, Alan; Owens, Jane; Okamura, Haruki; Kurimoto, Masahi; Chambers, Timothy J.; Martin, T. John; Gillespie, Matthew T.
CORPORATE SOURCE: St. Vincent's Institute Medical Research, University Melbourne, Fitzroy, 3065, Australia
SOURCE: J. Exp. Med. (1997), 185(6), 1005-1012
CODEN: JEMEAV; ISSN: 0022-1007
PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We have established by differential display polymerase chain reaction of mRNA that interleukin (**IL**)-**18** is expressed by osteoblastic stromal cells. The stromal cell populations used for comparison differed in their ability to promote **osteoclast**-like multinucleated cell (OCL) formation. MRNA for **IL-18** was found to be expressed in greater abundance in lines that were unable to support OCL formation than in supportive cells. Recombinant **IL-18** was found to inhibit OCL formation in cocultures of osteoblasts and hemopoietic cells of spleen or bone marrow origin. **IL-18** inhibited OCL formation in the presence of **osteoclastogenic** agents including 1.alpha.,25-dihydroxyvitamin D3, prostaglandin E2, parathyroid hormone, IL-1, and IL-11. The inhibitory effect of **IL-18** was limited to the early phase of the cocultures, which coincides with proliferation of hemopoietic precursors. **IL-18** has been reported to induce interferon-.gamma. (IFN-.gamma.) and granulocyte/macrophage colony-stimulating factor (GM-CSF) prodn. in T cells, and both agents also inhibit OCL formation in vitro. Neutralizing antibodies to GM-CSF were able to rescue **IL-18** inhibition of OCL formation, whereas neutralizing antibodies

to IFN-.gamma. did not. In cocultures with osteoblasts and spleen cells from IFN-.gamma. receptor type II-deficient mice, **IL-18** was found to inhibit OCL formation, indicating that **IL-18** acted independently of IFN-.gamma. prodn.: IFN-.gamma. had no effect in these cocultures. Addnl., in cocultures in which spleen cells were derived from receptor-deficient mice and osteoblasts were from wild-type mice and vice versa, we identified that the target cells for IFN-.gamma. inhibition of OCL formation were the hemopoietic cells. This work provides evidence that **IL-18** is expressed by osteoblasts and inhibits OCL formation via GM-CSF prodn. and not via IFN-.gamma. prodn.

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=> fil reg

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STRUCTURE FILE UPDATES:   18 JUN  99  HIGHEST RN 225531-94-2
DICTIONARY FILE UPDATES:  23 JUN  99  HIGHEST RN 225531-94-2

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=> s (ndqvlf|fedmtd|fklilkk|mykds|stlsc)/sqsp

L7           96 NDQVLF|FEDMTD|FKLILKK|MYKDS|STLSC/SQSP

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=> fil hcaplus

FILE 'HCAPLUS' ENTERED AT 14:30:40 ON 23 JUN 1999
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FILE COVERS 1967 - 23 Jun 1999  VOL 130 ISS 26
FILE LAST UPDATED: 23 Jun 1999  (19990623/ED)

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L8           85 L7

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L3            221 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L1 OR (INTERLEUKIN OR
                  IL)(W)18 OR IGIF? OR INTERFERON(W)GAMMA(W)INDUCING(W)FACTOR
L4           4126 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L2 OR OSTEOCLAST?
L5              4 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L3 AND L4
L7             96 SEA FILE=REGISTRY ABB=ON  PLU=ON  NDQVLF|FEDMTD|FKLILKK|MYKDS|S
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L8             85 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L7
L9              1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L8 AND L4
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L2            262 SEA FILE=REGISTRY ABB=ON  PLU=ON  OSTEOCLAST/BI
L3            221 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L1 OR (INTERLEUKIN OR
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L4           4126 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L2 OR OSTEOCLAST?
L5              4 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L3 AND L4
L11             7 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L3(L)BONE
L12             3 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L11 NOT L5

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L12 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1998:693778 HCAPLUS
DOCUMENT NUMBER: 129:289007
TITLE: Production of functional IL-18 by different subtypes of murine and human dendritic cells (DC). DC-derived IL-18 enhances IL-12-dependent Th1 development
AUTHOR(S): Stoll, Sabine; Jonuleit, Helmut; Schmitt, Edgar; Mueller, Gabriele; Yamauchi, Hiroshi; Kurimoto, Masashi; Knop, Juergen; Enk, Alexander H.
CORPORATE SOURCE: Clinical Research Unit, Department Dermatology, University Mainz, Mainz, D-55131, Germany
SOURCE: Eur. J. Immunol. (1998), 28(10), 3231-3239
CODEN: EJIMAF; ISSN: 0014-2980
PUBLISHER: Wiley-VCH Verlag GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **IL-18** is a cytokine that shares biol. activities with IL-12 in driving the development of Th1-type T cells. As dendritic cells (DC) are very potent inducers of T cell proliferation and differentiation the authors wondered whether they utilize **IL-18** as a factor driving Th1 development. The authors demonstrate by Northern blot and reverse transcription-PCR that various subtypes of human and murine DC as well as the DC-line XS contain **IL-18** mRNA. When supernatants of either enriched Langerhans cells (LC) or **bone** marrow-derived DC were analyzed for prodn. of **IL-18**

protein, **IL-18** prodn. was detected in an **IL-18**-specific ELISA. To assess whether the **IL-18** protein released by DC is functional, the authors performed a sensitive bioassay using the **IL-18**-dependent stimulation of Con A-stimulated T cells. Supernatants from **bone** marrow-derived DC and enriched LC induced IFN-.gamma. prodn. in the T cells. This prodn. was partially inhibitable by addn. of anti-**IL-18** antiserum. In a TCR-transgenic mouse system the authors demonstrate that DC-derived **IL-18** potentiates IL-12-dependent Th1 development. Using DC derived from IL-12 knockout animals, the authors show that DC-derived **IL-18** by itself is not capable of inducing Th1 cell differentiation. The data demonstrate that subtypes of DC are able to release functional **IL-18** that is able to induce IFN-.gamma. prodn. and Th1 differentiation in primed T cells.

L12 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER:	1998:403581 HCAPLUS
DOCUMENT NUMBER:	129:135004
TITLE:	Murine macrophages secrete interferon .gamma. upon combined stimulation with interleukin (IL)-12 and IL-18: a novel pathway of autocrine macrophage activation
AUTHOR(S):	Munder, Markus; Mallo, Moises; Eichmann, Klaus; Modolell, Manuel
CORPORATE SOURCE:	Max-Planck-Inst. Immunbiol., Freiburg, D-79108, Germany
SOURCE:	J. Exp. Med. (1998), 187(12), 2103-2108 CODEN: JEMEAV; ISSN: 0022-1007
PUBLISHER:	Rockefeller University Press
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB Interferon (IFN)-.gamma., a key immunoregulatory cytokine, has been thought to be produced solely by activated T cells and natural killer cells. In this study, we show that murine **bone** marrow derived macrophages (BMM.PHI.) secrete large amts. of IFN-.gamma. upon appropriate stimulation. Although interleukin (IL)-12 and **IL-18** alone induce low levels of IFN-.gamma. mRNA transcripts, the combined stimulation of BMM.PHI. with both cytokines leads to the efficient prodn. of IFN-.gamma. protein. The macrophage-derived IFN-.gamma. is biol. active as shown by induction of inducible nitric oxide synthase as well as upregulation of CD40 in macrophages. Our findings uncover a novel pathway of autocrine macrophage activation by demonstrating that the macrophage is not only a key cell type responding to IFN-.gamma. but also a potent IFN-.gamma.-producing cell.

L12 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER:	1995:566376 HCAPLUS
DOCUMENT NUMBER:	123:30912
TITLE:	Monoclonal antibodies identifying feline hemopoietic cell lineages
AUTHOR(S):	Groshek, P. M.; Dean, G. A.; Hoover, E. A.
CORPORATE SOURCE:	College Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, CO, USA
SOURCE:	Comp. Haematol. Int. (1994), 4(4), 181-91 CODEN: CHAIEX; ISSN: 0938-7714
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB Monoclonal antibodies (MAbs) were prepd. against feline **bone** marrow mononuclear cells. Immunogold immunofluorescence (**IGIF**), flow cytometry and fluorescence activated cell sorting (FACS) were used to det. the selective reactivity of four MAbs, designated FeMy, FeLy and FeEr1/Er2 with feline myeloid (granulocyte/macrophage), lymphoid, and erythroid lineage cells, resp. Reactivity was also assessed to four feline lymphoma cell lines (3201, 3191, 3281, FL74). FeMy reacted with 74% of all myeloid lineage cells (88% of mature and 30% of early myeloid progenitors), 98% of blood neutrophils, 97% of eosinophils and 90% of

monocytes. FACS of **bone** marrow using FeMy yielded 89% myeloid lineage cells. FeLy reacted with 67-75% of lymphoid lineage marrow cells **IGIF** and flow cytometry. However, FeLy also recognized a surface mol. present on 30% of erythroid precursors, 86% of eosinophils, and three of four feline lymphoma cell lines. FACS of marrow cells using FeLy yielded 77% lymphoid cells (and 19% myeloid cells). FeEr1 and FeEr2 (which identified either the same or closely assocd. mols.) reacted with 55-66% of early erythroid and 90-95% of late erythroid lineage marrow cells but not with mature erythrocytes by immunogold immunofluorescence. Marrow FACS using FeEr1 and FeEr2 yielded 76-80% erythroid cells (and 18-21% myeloid progenitors). Wheres FeLy immunopptd. a 120 kDa mol., neither FeMy nor FeEr1 and FeEr2 pptd. an identifiable mol. The panel of MAbs described may be useful in immunophenotyping of feline hemopoietic neoplasia.

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=> d stat que

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L3          221 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L1 OR (INTERLEUKIN OR
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L4         4126 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L2 OR OSTEOCLAST?
L5            4 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L3 AND L4
L7           96 SEA FILE=REGISTRY ABB=ON  PLU=ON  NDQVLF|FEDMTD|FKLILKK|MYKDS|S
                TLSC/SQSP
L8           85 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L7
L11           7 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L3(L)BONE
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=> d stat que l15

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L4         4126 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L2 OR OSTEOCLAST?
L5            4 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L3 AND L4
L7           96 SEA FILE=REGISTRY ABB=ON  PLU=ON  NDQVLF|FEDMTD|FKLILKK|MYKDS|S
                TLSC/SQSP
L8           85 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L7
L11           7 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L3(L)BONE
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L14          17 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L8 AND L3
L15          16 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L14 NOT (L5 OR L12)

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L15 ANSWER 1 OF 16 HCAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1999:127022 HCAPLUS
DOCUMENT NUMBER: 130:195766
TITLE: Cloning of cDNAs for canine **interleukin 18** (**IL-18**) and canine interleukin 1.beta. convertase (ICE) and use of **IL-18** and ICE for treating canine immunological diseases

INVENTOR(S): Okano, Fumiyoshi
PATENT ASSIGNEE(S): Toray Industries, Inc., Japan
SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9907851	A1	19990218	WO 98-JP3524	19980807
W: AU, CA, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9885611	A1	19990301	AU 98-85611	19980807

PRIORITY APPLN. INFO.: JP 97-213754 19970807
WO 98-JP3524 19980807

AB The cDNAs encoding canine **IL-18** and ICE are isolated from a cDNA library prepd. from the canine spleen cells stimulated with chicken Newcastle Disease Virus by using primers derived from mouse **IL-18** and human ICE, resp. Recombinant prepn. of active **IL-18** in transgenic Escherichia coli and silkworms, without the expression of ICE, was shown. Antitumor activity of **IL-18** prepd. from transgenic silkworms was also demonstrated.

IT **220792-18-7P**
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(amino acid sequence; cloning of cDNAs for canine **interleukin 18** (**IL-18**) and canine interleukin 1.beta. convertase (ICE) and use of **IL-18** and ICE for treating canine immunol. diseases)

L15 ANSWER 2 OF 16 HCAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1999:112589 HCAPLUS
DOCUMENT NUMBER: 130:310438
TITLE: Cloning of cDNA for canine **interleukin-18** and canine interleukin-1.beta. converting enzyme and expression of canine **interleukin-18**
AUTHOR(S): Okano, Fumiyoshi; Satoh, Masahiro; Ido, Takayoshi; Yamada, Katsushige
CORPORATE SOURCE: Chemicals Research Laboratories, Toray Industries, Inc., Nagoya, Japan
SOURCE: J. Interferon Cytokine Res. (1999), 19(1), 27-32
CODEN: JICRFJ; ISSN: 1079-9907
PUBLISHER: Mary Ann Liebert, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cloning of canine **interleukin-18** (**IL-18**) and canine interleukin-1.beta. converting enzyme (ICE) cDNA was carried out by using murine **IL-18** cDNA and human ICE cDNA, resp., as probes. Sequence homol. to known sequences of human, mouse, or rat genes was noted at nucleotide and amino acid levels. Canine **IL-18** mRNA was expressed in various canine organs, whereas canine ICE mRNA was expressed in only a few, particularly in the brain and testis. Cloned canine **IL-18** cDNA was expressed in Escherichia coli. The resulting protein promoted induction of canine interferon-.gamma. (IFN-.gamma.) from stimulated canine lymphocytes. Canine **IL-18** and canine IL-12 produced canine IFN-.gamma. synergistically. Canine **IL-18** suppressed the growth of tumor cells transplanted in SCID mice. Cloned canine **IL-18** should prove useful as an anticancer agent.

IT **220792-18-7, Interleukin 18** (Canis familiaris)
RL: PRP (Properties)
(amino acid sequence; **interleukin-18** and interleukin-1.beta. converting enzyme cDNA sequences of dog, tissue-specific expression, and canine **interleukin-18** expression in Escherichia coli and anti-tumor effects)

L15 ANSWER 3 OF 16 HCAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1998:466352 HCAPLUS
DOCUMENT NUMBER: 129:108017
TITLE: **Interleukin-18**-receptor proteins
INVENTOR(S): Torigoe, Kakuji; Ushio, Shimpei; Kunikata, Toshio; Kurimoto, Masashi
PATENT ASSIGNEE(S): Kabushiki Kaisha Hayashibara Seibutsu Kagaku Kenkyujo, Japan
SOURCE: Eur. Pat. Appl., 35 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 850952	A1	19980701	EP 97-310555	19971223
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AU 9749224	A1	19980702	AU 97-49224	19971223
JP 11100400	A2	19990413	JP 97-366674	19971226
PRIORITY APPLN. INFO.:			JP 96-356426	19961226
			JP 97-52526	19970221
			JP 97-163490	19970606
			JP 97-215490	19970728

AB Disclosed are a receptor protein which recognize a novel cytokine, i.e., **interleukin-18**, a monoclonal antibody specific to the protein, and uses thereof. The receptor protein is useful as pharmaceutical to treat and prevent autoimmune and allergic disease because it suppresses and regulates excessive immunoreaction. The monoclonal antibody specifically reacts with **interleukin-18**, exhibiting efficacy in purifn., detection and inhibition of **interleukin-18**.

IT **189304-54-9 208197-35-7, Interleukin 18** (mouse) **210042-65-2, Interleukin 18** [73-methionine] (human) **210042-75-4, Interleukin 18** [70-threonine] (mouse)
RL: PRP (Properties)
(amino acid sequence; **interleukin-18**-receptor proteins for preventing autoimmune diseases and allergic diseases and monoclonal antibody)

L15 ANSWER 4 OF 16 HCAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1998:365121 HCAPLUS
DOCUMENT NUMBER: 129:66847
TITLE: **Interferon .gamma.-inducing factor variants** with improved stability and activity
INVENTOR(S): Yamamoto, Kozo; Okamoto, Iwao; Kurimoto, Masashi
PATENT ASSIGNEE(S): Kabushiki Kaisha Hayashibara Seibutsu Kagaku Kenkyujo, Japan
SOURCE: Eur. Pat. Appl., 59 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 845530	A2	19980603	EP 97-309632	19971128

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

PRIORITY APPLN. INFO.: JP 96-333037 19961129
JP 97-20906 19970121
JP 97-329715 19971114

AB Disclosed are created stable polypeptide (**interleukin 18**) variants which are capable of inducing the prodn. of interferon-.gamma. by immunocompetent cells. The present polypeptides contain specific amino acid sequences usually derived from the wild-type polypeptides, being capable of the prodn. of interferon-.gamma., by replacing the cysteine(s) with different amino acid(s). The present polypeptides possess a stability and an activity of inducing the prodn. of interferon-.gamma. by immunocompetent cells, both of which are significantly higher than those of the wild-type polypeptides. In addn. to the interferon-.gamma. induction, the polypeptides can exhibit remarkable activities of inducing the formation of killer cells and enhancing their cytotoxicities. The present polypeptides are easily obtainable by oligonucleotide-directed site-specific mutagenesis using recombinant DNA techniques. Thus, the present polypeptides are useful for agents to treat and/or prevent susceptive diseases such as viral diseases, infections, malignant tumors, and immunopathies.

IT **189304-55-0DP, Interleukin 18** (human), variants **208197-35-7DP, Interleukin 18** (mouse), variants **208204-46-0P, Interleukin 18** [68-serine] (human) **208204-47-1P 208204-48-2P 208204-49-3P 208204-50-6P 208204-51-7P 208204-52-8P 208204-53-9P, Interleukin 18** [7-alanine] (mouse) **208204-54-0P, Interleukin 18** [125-serine] (mouse)
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); PRP (Properties); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(amino acid sequence; **interferon .gamma.-inducing factor** variants with improved stability and activity)

IT **208125-70-6 208125-71-7 208125-72-8**
RL: BOC (Biological occurrence); PRP (Properties); BIOL (Biological study); OCCU (Occurrence)
(consensus partial sequence; **interferon .gamma.-inducing factor** variants with improved stability and activity)

L15 ANSWER 5 OF 16 HCAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1998:176021 HCAPLUS
DOCUMENT NUMBER: 128:229370
TITLE: **Interferon .gamma.-inducing factor** in rat neuroendocrine cells and its cDNA sequence
INVENTOR(S): Joh, Tong H.; Conti, Bruno
PATENT ASSIGNEE(S): Cornell Research Foundation, Inc., USA
SOURCE: PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9810072	A1	19980312	WO 97-US15891	19970908

W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE,

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            ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
            LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU,
            SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, AM, AZ,
            BY, KG, KZ, MD, RU, TJ, TM
        RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR,
            GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA,
            GN, ML, MR, NE, SN, TD, TG
     AU 9742604        A1   19980326       AU 97-42604       19970908
PRIORITY APPLN. INFO.:                     US 96-25141       19960909
                                           US 97-43087       19970408
                                           WO 97-US15891     19970908
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AB The present invention relates to isolated cDNA mols. encoding **interferon-.gamma. inducing factors** (**IGIF**), **interleukin-18** and **interleukin-18**.alpha., from rat. **Interleukin-18**.alpha. is a shorter isoform of **interleukin-18** which lacks a fragment comprising 57 nucleotide residues, a probable exon, and the corresponding 19 amino acids in the predicted protein. Both factors contain an N-terminal leader peptide of 36 amino acid residues. **IGIF** mRNA induction was strong and specific in both reserpine-treated and cold-stressed animals, whereas little or no signal was detected in control or in vehicle-treated animals; induction was localized to the adrenal cortex, specifically to the zona reticularis and fasciculata. Detection of **IGIF** or its mRNA by immunoassay or nucleic acid hybridization can be used to quantitate stress levels in an animal target.

IT **186847-61-0 186847-62-1**
RL: BOC (Biological occurrence); BPR (Biological process); PRP (Properties); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(amino acid sequence; **interferon .gamma.-inducing factor** in rat neuroendocrine cells and its cDNA sequence)

L15 ANSWER 6 OF 16 HCAPLUS COPYRIGHT 1999 ACS

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ACCESSION NUMBER:        1998:133621  HCAPLUS
DOCUMENT NUMBER:         128:166370
TITLE:                   Preparation of an interferon-gamma inducing
                         polypeptide
INVENTOR(S):             Tanimoto, Tadao; Kurimoto, Masashi
PATENT ASSIGNEE(S):      Kabushiki Kaisha Hayashibara Seibutsu Kagaku Kenkyujo,
                         Japan
SOURCE:                  Eur. Pat. Appl., 18 pp.
                         CODEN: EPXXDW
DOCUMENT TYPE:           Patent
LANGUAGE:                English
FAMILY ACC. NUM. COUNT:  1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE          APPLICATION NO.  DATE
     ---------------   ----  --------      ---------------  --------
     EP 821005         A2    19980128      EP 97-305376     19970718
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, FI
     US 5891663        A     19990406      US 97-896501     19970718
     JP 10271998       A2    19981013      JP 97-213385     19970725
PRIORITY APPLN. INFO.:                     JP 96-213267     19960725
                                           JP 97-31474      19970131
```

AB A method for converting a precursor of a polypeptide that induces IFN-.gamma. prodn. in immunocompetent cells, characterized in that it comprises a step of contacting an interleukin-1.beta. converting enzyme with the precursor to convert it into an active polypeptide that induces IFN-.gamma. prodn. in immunocompetent cells. PKCHuGF contg. precursor polypeptide and pCDHICE encoding interleukin 1.beta.-converting enzyme were prepd., and active polypeptide contg. Tyr-Phe-Gly-Lys-Leu at the N-terminal region was purified for inducing prodn. of interferon .gamma..

IT **178234-94-1, Interleukin 18** (human)

189304-54-9 189304-55-0 202608-43-3
RL: PRP (Properties)
(amino acid sequence; prepn. of .gamma. interferon prodn.-inducing polypeptide and interleukin 1.beta.-converting enzyme)

L15 ANSWER 7 OF 16 HCAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1998:133533 HCAPLUS
DOCUMENT NUMBER: 128:151108
TITLE: Enzyme which activates an interferon-.gamma. inducing polypeptide
INVENTOR(S): Tanimoto, Tadao; Kurimoto, Masashi
PATENT ASSIGNEE(S): Kabushiki Kaisha Hayashibara Seibutsu Kagaku Kenkyujo, Japan
SOURCE: Eur. Pat. Appl., 18 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 819757	A2	19980121	EP 97-305377	19970718
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 10080270	A2	19980331	JP 97-156062	19970530
US 5879942	A	19990309	US 97-896605	19970718
PRIORITY APPLN. INFO.:			JP 96-207691	19960719
			JP 97-156062	19970530

AB An enzyme or a protein is disclosed which converts a precursor of a polypeptide that induces IFN-.gamma. prodn. in an immunocompetent cell into the active form. The enzyme is produced from proliferating cells (THP-1, U-939, or HL-60 cells) and purified by (NH4)2SO4 pptn., and chromatog. on DEAD 5PW, S-Sepharose, Mono S, and Superdex 200 columns. The enzyme activates the INF-.gamma.-inducing precursor protein by cleavage of the bond between Asp36 and Tyr37, has a mol. wt. of about 25,000 Da and about 10,000 Da on SDS-PAGE, and is inhibited by iodoacetamide and Ac-YVAD-CHO. Partial amino acid sequences are provided for peptide fragments of the enzyme.

IT **189304-54-9P 189304-55-0P**
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(enzyme which activates an interferon-.gamma. inducing polypeptide)

IT **178234-94-1, Interleukin 18** (human)
202608-43-3
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(enzyme which activates an interferon-.gamma. inducing polypeptide)

L15 ANSWER 8 OF 16 HCAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1998:116142 HCAPLUS
DOCUMENT NUMBER: 128:137190
TITLE: Genomic DNA encoding a polypeptide capable of inducing the production of interferon-.gamma.
INVENTOR(S): Okura, Takanori; Torigoe, Kakuji; Kurimoto, Masashi
PATENT ASSIGNEE(S): Kabushiki Kaisha Hayashibara Seibutsu Kagaku Kenkyujo, Japan
SOURCE: Eur. Pat. Appl., 74 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 816499	A2	19980107	EP 97-304616	19970627

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        R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
            IE, FI
     JP 10080288       A2   19980331        JP 97-187418     19970627
PRIORITY APPLN. INFO.:                      JP 96-185305     19960627
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AB Disclosed is a human genomic DNA encoding a polypeptide capable of inducing the prodn. of interferon-.gamma. by immunocompetent cells. The gene comprises at least 5 introns and 6 exons, and a sequence of 28,994 bp was detd. for the gene, including an extensive 5'-flanking region. The genomic DNA efficiently expresses the polypeptide with high biol. activities of such as inducing the prodn. of interferon-.gamma. by immunocompetent cells, enhancing killer cells' cytotoxicity and inducing killer cells' formation, when introduced into mammalian host cells. Recombinant plasmid vectors are constructed for expression of the polypeptide in Escherichia coli and CHO cells. The high biol. activities of the polypeptide facilitate its uses to treat and/or prevent malignant tumors, viral diseases, bacterial infectious diseases and immune diseases without serious side effects when administered to humans.

IT **178254-42-7P 178254-43-8P 189304-54-9P**, Protein [73-isoleucine] (human interferon .gamma.-inducing) **189304-55-0P**, Protein [73-threonine] (human interferon .gamma.-inducing)
RL: BPN (Biosynthetic preparation); PRP (Properties); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(amino acid sequence; genomic DNA encoding a polypeptide capable of inducing the prodn. of interferon-.gamma.)

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L15  ANSWER 9 OF 16  HCAPLUS  COPYRIGHT 1999 ACS
ACCESSION NUMBER:         1997:776271  HCAPLUS
DOCUMENT NUMBER:          128:58316
TITLE:                    Human interleukin-1.gamma. and antagonists thereof
INVENTOR(S):              Sana, Theodore R.; Timans, Jacqueline C.; Hardiman,
                          Gerard T.; Kastelein, Robert A.; Bazan, J. Fernando
PATENT ASSIGNEE(S):       Schering Corporation, USA
SOURCE:                   PCT Int. Appl., 62 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.       KIND  DATE           APPLICATION NO.  DATE
     ---------------  ----  --------       ---------------  --------
     WO 9744468        A1   19971127       WO 97-US7282     19970516
         W:  AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CZ, EE, GE, HU, IL,
             IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO,
             NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, UZ, VN, YU, AM,
             AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB,
             GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN,
             ML, MR, NE, SN, TD, TG
     AU 9731166        A1   19971209       AU 97-31166      19970516
     EP 914453         A1   19990512       EP 97-926391     19970516
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE,
             LT, LV, FI, RO
PRIORITY APPLN. INFO.:                     US 96-651998     19960520
                                           WO 97-US7282     19970516
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AB Nucleic acids encoding human IL-1.gamma., and purified IL-1.gamma. proteins and fragments thereof are provided. Polyclonal and monoclonal antibodies, both anti-IL-1.gamma. antibodies and anti-idiotypic antibodies which may be agonists or antagonists of human IL-1.gamma., are also provided. Methods of using the compns. for both diagnostic and therapeutic utilities are also provided, together with antagonists and receptors of human IL-1.gamma..

IT **178234-94-1, Interleukin 18** (human)
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL

(Biological study)
(amino acid sequence; structure and antagonists of human interleukin-1.gamma.)

L15 ANSWER 10 OF 16 HCAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1997:689145 HCAPLUS
DOCUMENT NUMBER: 127:357917
TITLE: Involvement of caspase-1 and caspase-3 in the production and processing of mature human **interleukin 18** in monocytic THP.1 cells
AUTHOR(S): Akita, Kenji; Ohtsuki, Takashi; Nukada, Yoshiyuki; Tanimoto, Tadao; Namba, Motoshi; Okura, Takanori; Takakura-Yamamoto, Rohko; Torigoe, Kakuji; Gu, Yong; Su, Michael S. -S.; Fujii, Mitsukiyo; Satoh-Itoh, Michiyo; Yamamoto, Kouzo; Kohno, Keizo; Ikeda, Masao; Kurimoto, Masashi
CORPORATE SOURCE: Fujisaki Institute, Hayashibara Biochemical Laboratories, Inc., Okayama, 702, Japan
SOURCE: J. Biol. Chem. (1997), 272(42), 26595-26603
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Recently, human **interleukin 18** (hIL-18) cDNA was cloned, and the recombinant protein with a tentatively assigned N-terminal amino acid sequence was generated. However, natural hIL-18 has not yet been isolated, and its cellular processing is therefore still unclear. To clarify this, the authors purified natural hIL-18 from the cytosolic ext. of monocytic THP.1 cells. Natural hIL-18 exhibited a mol. mass of 18.2 kDa, and the N-terminal amino acid was Tyr37. Biol. activities of the purified protein were identical to those of recombinant hIL-18 with respect to the enhancement of natural killer cell cytotoxicity and interferon-.gamma. prodn. by human peripheral blood mononuclear cells. The authors also found two precursor hIL-18 (prohIL-18)-processing activities in the cytosol of THP.1 cells. These activities were blocked sep. by the caspase inhibitors Ac-YVAD-CHO and Ac-DEVD-CHO. Further analyses of the partially purified enzymes revealed that one is caspase-1, which cleaves prohIL-18 at the Asp36-Tyr37 site to generate the mature hIL-18, and the other is caspase-3, which cleaves both precursor and mature hIL-18 at Asp71-Ser72 and Asp76-Asn77 to generate biol. inactive products. Apparently, the prodn. and processing of natural hIL-18 are regulated by two processing enzymes, caspase-1 and caspase-3, in THP.1 cells.

IT **178234-94-1, Interleukin 18** (human)
RL: PRP (Properties)
(caspase-1 and caspase-3 in formation and processing of mature human **interleukin 18** in monocytes)

L15 ANSWER 11 OF 16 HCAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1997:526678 HCAPLUS
DOCUMENT NUMBER: 127:148349
TITLE: Human **interferon .gamma.- inducing factor**-2 cDNA sequence, point mutation, and drug screening and disease diagnosis and therapy
INVENTOR(S): Coleman, Roger; Cocks, Benjamin Graeme; Hawkins, Phillip R.
PATENT ASSIGNEE(S): Incyte Pharmaceuticals, Inc., USA; Coleman, Roger; Cocks, Benjamin Graeme; Hawkins, Phillip R.
SOURCE: PCT Int. Appl., 59 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUMBER COUNT: 1

PATENT INFORMATION:

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     PATENT NO.        KIND  DATE          APPLICATION NO.  DATE
     ---------------   ----  --------      ---------------  --------
     WO 9724441         A1   19970710      WO 96-US20432    19961220
         W:  AT, AU, BA, BR, CA, CH, CN, DE, DK, ES, FI, GB, IL, JP, KR, LC,
             MX, NO, NZ, RU, SE, SG, US, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR,
             IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML,
             MR, NE, SN, TD, TG
     CA 2238885         AA   19970710      CA 96-2238885    19961220
     AU 9713417         A1   19970728      AU 97-13417      19961220
     EP 870028          A1   19981014      EP 96-944936     19961220
         R:  BE, DE, ES, FR, GB, IT, NL
PRIORITY APPLN. INFO.:                     US 95-580667     19951229
                                           WO 96-US20432    19961220
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AB The present invention provides a polynucleotide (**igif**-2) which identifies and encodes a novel **interferon .gamma.-inducing factor**-2 (**IGIF**-2) which was expressed in adenoid, brain, kidney, liver, lung, skin, synovium, and T-lymphocytes. The present invention also provides for antisense mols. The invention further provides genetically engineered expression vectors and host cells for the prodn. of purified **IGIF**-2; antibodies, antagonists and inhibitors; and pharmaceutical compns. and methods of treatment based on the polypeptide, its antibodies, antagonists and inhibitors. The invention specifically provides for use of this polypeptide as therapeutic for immunocompromised individuals and as a pos. control in diagnostic assays for the detection of aberrant **IGIF**-2 expression or altered leukocyte or lymphocyte activity.

IT **178234-94-1P, Interleukin 18** (human)
193294-40-5P 193294-41-6P
RL: ANT (Analyte); ARU (Analytical role, unclassified); BOC (Biological occurrence); BPN (Biosynthetic preparation); BPR (Biological process); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); PROC (Process); USES (Uses)
(amino acid sequence; human **interferon .gamma.-inducing factor**-2 cDNA sequence, point mutation, and drug screening and disease diagnosis and therapy)

L15 ANSWER 12 OF 16 HCAPLUS COPYRIGHT 1999 ACS

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ACCESSION NUMBER:        1997:342328  HCAPLUS
DOCUMENT NUMBER:         126:316334
TITLE:                   Protein which induces interferon-gamma production by
                         immunocompetent cell
INVENTOR(S):             Akita, Kenji; Nukada, Yoshiyuji; Fujii, Mitsukiyo;
                         Tanimoto, Tadao; Kurimoto, Masashi
PATENT ASSIGNEE(S):      Kabushiki Kaisha Hayashibara Seibutsu Kagaku Kenkyujo,
                         Japan
SOURCE:                  Eur. Pat. Appl., 26 pp.
                         CODEN: EPXXDW
DOCUMENT TYPE:           Patent
LANGUAGE:                English
FAMILY ACC. NUM. COUNT:  1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE          APPLICATION NO.  DATE
     ---------------   ----  --------      ---------------  --------
     EP 767178          A1   19970409      EP 96-306997     19960926
         R:  BE, CH, DE, DK, ES, FR, GB, IT, LI, NL, SE
     JP 09289896        A2   19971111      JP 96-269105     19960920
     CA 2186423         AA   19970327      CA 96-2186423    19960925
     AU 9665881         A1   19970515      AU 96-65881      19960926
PRIORITY APPLN. INFO.:                     JP 95-270725     19950926
                                           JP 96-67434      19960229
                                           JP 96-269105     19960920
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AB A protein of human cell origin, which induces the IFN-.gamma. prodn. by immunocompetent cells and has the amino acid sequence near or at the N-terminus detd. The protein is purified from human hematopoietic cells, such as lymphoblasts, lymphocytes, monoblasts, monocytes, myeloblasts, myelocytes, granulocytes and macrophages. The protein also induces formation of NK cells, enhances cytotoxicity of NK cells, and can be used for preventing and/or treating IFN-.gamma. susceptive diseases. Compn. contg. the protein and interleukin 2, stabilizer, antioncotic agent, antitumor agent, antiviral agent, antibacterial agent or interleukin 12 is also disclosed for treating atopic diseases. The protein of the invention was isolated from THP-1, KG-1, HeLa and A-253 cells, partial sequence detd., stimulation of interferon .gamma. prodn. and induction of NK cell cytotoxicity and others were characterized, and use of the protein to prep. immunocompetent cells for adoptive immunotherapy was described.

IT **189304-54-9 189304-55-0**
RL: PRP (Properties)
(amino acid sequence; human hematopoietic cell-derived protein which induces interferon-gamma prodn. by immunocompetent cell for treating atopic disease)

IT **189265-23-4 189326-26-9**
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(human hematopoietic cell-derived protein which induces interferon-gamma prodn. by immunocompetent cell for treating atopic disease)

L15 ANSWER 13 OF 16 HCAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1997:80706 HCAPLUS
DOCUMENT NUMBER: 126:156262
TITLE: Induction of **interferon-.gamma. inducing factor** in the adrenal cortex
AUTHOR(S): Conti, Bruno; Jahng, Jeong Won; Tinti, Cristina; Son, Jin H.; Joh, Tong H.
CORPORATE SOURCE: Laboratory Molecular Neurobiology, Cornell Univ. Medical College, White Plains, NY, 10605, USA
SOURCE: J. Biol. Chem. (1997), 272(4), 2035-2037
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Interferon-.gamma. inducing factor** (**IGIF**) is a recently identified cytokine also called interleukin-1.gamma. (IL-1.gamma.) or **interleukin-18** (**IL-18**). Its biol. activity is pleiotropic, and, so far, it has been shown to induce interferon-.gamma. prodn. in Th1 cells, to augment the prodn. of granulocyte-macrophage-CSF, and to decrease that of interleukin-10 (IL-10). The authors first detected newly synthesized **IGIF** mRNA by differential display in the adrenal gland of reserpine-treated rats and then isolated two transcripts by reverse transcription polymerase chain reaction. They were identified as rat **IGIF** on the basis of the high homol. with mouse: 91% at both the nucleotide and the amino acid level. Subsequently, the authors investigated the effects of stress on **IGIF** mRNA levels and found that acute cold stress strongly induced **IGIF** gene expression. In situ hybridization anal. showed that **IGIF** is synthesized in the adrenal cortex, specifically in the zona reticularis and fasciculata that produce glucocorticoids. The presence of **IGIF** mRNA was also detected in the neurohypophysis although induction by stress was not significant. The authors' results call for more attention to the role of the adrenal gland as a potential effector of immunomodulation and suggest that **IGIF** itself might be a secreted neuroimmunomodulator and play an important role in orchestrating the immune system following a stressful experience.

IT **186847-61-0 186847-62-1**

RL: PRP (Properties)
(amino acid sequence; sequence and induction of **interferon-.gamma. inducing factor** in adrenal cortex and presence in neurohypophysis in relation to cold stress)

L15 ANSWER 14 OF 16 HCAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1996:397243 HCAPLUS
DOCUMENT NUMBER: 125:84660
TITLE: A peptide inducer of interferon .gamma. synthesis and antibodies against and their use in the treatment of interferon .gamma.-susceptible disease
INVENTOR(S): Ushio, Shimpei; Torigoe, Kakuji; Tanimoto, Tadao; Okamura, Haruki; Kunikata, Toshio; Taniguchi, Mutsuko; Kohno, Keizo; Fukuda, Shigeharu; Kurimoto, Masashi
PATENT ASSIGNEE(S): Kabushiki Kaisha Hayashibara Seibutsu Kagaku Kenkyujo, Japan
SOURCE: Eur. Pat. Appl., 48 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 712931	A2	19960522	EP 95-308055	19951110
EP 712931	A3	19970326		
R: BE, CH, DE, DK, ES, FR, GB, IT, LI, NL, SE				
JP 08231598	A2	19960910	JP 95-58240	19950223
JP 08193098	A2	19960730	JP 95-262062	19950918
JP 2724987	B2	19980309		
JP 10007699	A2	19980113	JP 97-58547	19950918
CA 2162353	AA	19960516	CA 95-2162353	19951107
AU 9537796	A1	19960523	AU 95-37796	19951113
AU 700948	B2	19990114		
JP 09157180	A2	19970617	JP 96-[illegible]	19960124

PRIORITY APPLN. INFO.:
JP 94-304203 19941115
JP 95-58240 19950223
JP 95-78357 19950310
JP 95-262062 19950918
JP 95-274968 19950929
JP 95-279906 19951004

AB A polypeptide of 18,500.+-.3,000 Da by SDS-PAGE and a pI of 4.9.+-.1.0 by chromatofocusing that strongly induces the IFN-.gamma. prodn. by immunocompetent cells at low concns. and that does not cause serious side effects even when administered to human in a relatively high dose is described. The protein is readily prepd. by immune affinity chromatog. using a monoclonal antibody and can be incorporated into agents for treating and/or preventing malignant tumors, viral diseases, bacterial infectious diseases, and immune diseases.

IT **174066-57-0P 178254-42-7P 178254-43-8P**
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); PRP (Properties); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); USES (Uses)
(amino acid sequence; peptide inducers of interferon .gamma. synthesis of human and mouse and antibodies against and their use in treatment of interferon .gamma.-susceptible disease)

L15 ANSWER 15 OF 16 HCAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1996:314489 HCAPLUS
DOCUMENT NUMBER: 125:55848
TITLE: Cloning of the cDNA for human IFN-.gamma.-inducing factor, expression in Escherichia coli, and studies on the biologic activities of the protein
AUTHOR(S): Ushio, Shimpei; Namba, Motoshi; Okura, Takanori;

Hattori, Kazuko; Nukada, Yoshiyuki; Akita, Kenji; Tanabe, Fujimi; Konishi, Kaori; Micallef, Mark; et al.
CORPORATE SOURCE: Fujisaki Inst., Hayashibara Biochem. Lab., Inc., Okayama, Japan
SOURCE: J. Immunol. (1996), 156(11), 4274-4279
CODEN: JOIMA3; ISSN: 0022-1767
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors have recently reported that a novel mol., murine IFN-.gamma.-inducing factor (**IGIF**) produced by mouse liver cells, possesses potent biol. activities, including the induction of IFN-.gamma. prodn. by spleen cells and the enhancement of NK cell cytotoxicity. In this paper, the authors report on the isolation of human **IGIF** cDNA clones from normal human liver cDNA libraries using murine **IGIF** cDNA as a probe. The amino acid sequence deduced from the human cDNA clones indicated a 193-amino acid precursor peptide and revealed 65% homol. with that of murine **IGIF**. The amino acid sequence of **IGIF** also included an IL-1 signature-like sequence. Subsequently, the cloned cDNA was expressed in Escherichia coli, and preliminary studies on the biol. activities of the recombinant protein were performed. The recombinant human **IGIF** induced IFN-.gamma. prodn. by mitogen-stimulated PBMC and enhanced NK cell cytotoxicity, in a manner similar to murine **IGIF**. In addn., recombinant human **IGIF** also augmented granulocyte-macrophage-CSF prodn. and decreased IL-10 prodn., but had no effect on IL-4 prodn. by Con A-stimulated PBMC. Based on these pleiotropic effects of **IGIF**, the authors propose that this novel cytokine be designated as **IL -18**.

IT **178234-94-1, Interleukin 18** (human)
RL: PRP (Properties)
(amino acid sequence; cloning of cDNA for human IFN-.gamma.-inducing factor, expression in Escherichia coli, and studies on biol. activities of protein)

L15 ANSWER 16 OF 16 HCAPLUS
ACCESSION NUMBER: 1995:908910 HCAPLUS
DOCUMENT NUMBER: 124:6762
TITLE: Cloning of a new cytokine that induces IFN-.gamma. production by T cells
AUTHOR(S): Okamura, Haruki; Tsutsui, Hiroko; Komatsu, Toshinori; Yutsudo, Masuo; Hakura, Akira; Tanimoto, Tadao; Torigoe, Kakuji; Okura, Takanori; Nukada, Yoshiyuki; et al.
CORPORATE SOURCE: Dep. Bacteriol., Hyogo Coll. Med., Nishinomiya, Japan
SOURCE: Nature (London) (1995), 378(6552), 88-91
CODEN: NATUAS; ISSN: 0028-0836
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The mechanism underlying the differentiation of CD4+ T cells into functionally distinct subsets (Th1 and Th2) is incompletely understood, and hitherto unidentified cytokines may be required for the functional maturation of these cells. Here the authors report the cloning of a recently identified IFN-.gamma.-inducing factor (**IGIF**) that augments natural killer (NK) activity in spleen cells. The gene encodes a precursor protein of 192 amino acids and a mature protein of 157 amino acids, which have no obvious similarities to any peptide in the databases. MRNAs for **IGIF** and interleukin-12 (IL-12) are readily detected in Kupffer cells and activated macrophages. Recombinant **IGIF** induces IFN-.gamma. more potently than does IL-12, apparently through a sep. pathway. Administration of anti-**IGIF** antibodies prevents liver damage in mice inoculated with Propionibacterium acnes and challenged with lipopolysaccharide, which induces toxic shock. **IGIF** may be involved in the development of Th1 cells and also in mechanisms of tissue injury in inflammatory reactions.

IT **171041-98-8**
RL: BAC (Biological activity or effector, except adverse); PRP

```
     (Properties); BIOL (Biological study)
        (amino acid sequence; sequence of interferon-.gamma.
        -inducing factor isolated from mouse liver that
        induces interferon-.gamma. formation by T-cells)

=>

=>

=> select hit rn l15 1-16

E1 THROUGH E30 ASSIGNED

=>

=>

=> fil reg

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=>

=>
=> d his l16


     (FILE 'HCAPLUS' ENTERED AT 14:30:40 ON 23 JUN 1999)
               SELECT HIT RN L15 1-16

     FILE 'REGISTRY' ENTERED AT 14:38:52 ON 23 JUN 1999
L16           30 S E1-E30 AND L7

=>

=>

=> d .seq l16 1-30


L16  ANSWER 1 OF 30  REGISTRY  COPYRIGHT 1999 ACS
RN   220792-18-7  REGISTRY
CN   Interleukin 18 (Canis familiaris) (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   Interleukin 18 (dog)
SQL  193
RN   220792-18-7  REGISTRY

SEQ      51 LNDQVLFVNE GNQPVFEDMP DSDCTDNAPH TIFIIYMYKD SLTRGLAVTI
             ======                                ==== =
        101 SVKYKTMSTL SCKNKTISFQ KMSPPDSIND EGNDIIFFQR SVPGHDDKIQ
                  === ==
HITS AT:    52-57, 87-91, 108-112

REFERENCE   1:  130:310438
```

REFERENCE 2: 130:195766

L16 ANSWER 2 OF 30 REGISTRY COPYRIGHT 1999 ACS
RN **210042-75-4** REGISTRY
CN Interleukin 18 [70-threonine] (mouse) (9CI) (CA INDEX NAME)
SQL 157
RN **210042-75-4** REGISTRY

```
SEQ       1 NFGRLHCTTA VIRNINDQVL FVDKRQPVFE DMTDIDQSAS EPQTRLIIYM
                           ===== =          == ====           =
         51 YKDSEVRGLA VTLSVKDSKT STLSCKNKII SFEEMDPPEN IDDIQSDLIF
            ====                 =====
        101 FQKRVPGHNK MEFESSLYEG HFLACQKEDD AFKLILKKKD ENGDKSVMFT
                                              =======
HITS AT:    16-21, 29-34, 50-54, 71-75, 132-138
```

REFERENCE 1: 129:108017

L16 ANSWER 3 OF 30 REGISTRY COPYRIGHT 1999 ACS
RN **210042-65-2** REGISTRY
CN Interleukin 18 [73-methionine] (human) (9CI) (CA INDEX NAME)
SQL 157
RN **210042-65-2** REGISTRY

```
SEQ       1 YFGKLESKLS VIRNLNDQVL FIDQGNRPLF EDMTDSDCRD NAPRTIFIIS
                           ===== =          = =====
         51 MYKDSQPRGM AVTISVKCEK ISMLSCENKI ISFKEMNPPD NIKDTKSDII
            =====
        101 FFQRSVPGHD NKMQFESSSY EGYFLACEKE RDLFKLILKK EDELGDRSIM
                                                =======
HITS AT:    16-21, 30-35, 51-55, 134-140
```

REFERENCE 1: 129:108017

L16 ANSWER 4 OF 30 REGISTRY COPYRIGHT 1999 ACS
RN **208204-54-0** REGISTRY
CN Interleukin 18 [125-serine] (mouse) (9CI) (CA INDEX NAME)
SQL 157
RN **208204-54-0** REGISTRY

```
SEQ       1 NFGRLHCTTA VIRNINDQVL FVDKRQPVFE DMTDIDQSAS EPQTRLIIYM
                           ===== =          == ====           =
         51 YKDSEVRGLA VTLSVKDSKM STLSCKNKII SFEEMDPPEN IDDIQSDLIF
            ====                 =====
        101 FQKRVPGHNK MEFESSLYEG HFLASQKEDD AFKLILKKKD ENGDKSVMFT
                                              =======
HITS AT:    16-21, 29-34, 50-54, 71-75, 132-138
```

REFERENCE 1: 129:66847

L16 ANSWER 5 OF 30 REGISTRY COPYRIGHT 1999 ACS
RN **208204-53-9** REGISTRY
CN Interleukin 18 [7-alanine] (mouse) (9CI) (CA INDEX NAME)
SQL 157
RN **208204-53-9** REGISTRY

```
SEQ       1 NFGRLHATTA VIRNINDQVL FVDKRQPVFE DMTDIDQSAS EPQTRLIIYM
                           ===== =          == ====           =
         51 YKDSEVRGLA VTLSVKDSKM STLSCKNKII SFEEMDPPEN IDDIQSDLIF
            ====                 =====
        101 FQKRVPGHNK MEFESSLYEG HFLACQKEDD AFKLILKKKD ENGDKSVMFT
                                              =======
HITS AT:    16-21, 29-34, 50-54, 71-75, 132-138
```

REFERENCE 1: 129:66847

```
L16  ANSWER 6 OF 30  REGISTRY  COPYRIGHT 1999 ACS
RN   208204-52-8  REGISTRY
CN   Interleukin 18 [38-serine,68-serine,76-alanine,127-serine] (human) (9CI)
     (CA INDEX NAME)
SQL  157
RN   208204-52-8  REGISTRY

SEQ       1 YFGKLESKLS VIRNLNDQVL FIDQGNRPLF EDMTDSDSRD NAPRTIFIIS
                           ===== =         = =====
         51 MYKDSQPRGM AVTISVKSEK ISTLSAENKI ISFKEMNPPD NIKDTKSDII
            =====
        101 FFQRSVPGHD NKMQFESSSY EGYFLASEKE RDLFKLILKK EDELGDRSIM
                                              =======
HITS AT:   16-21, 30-35, 51-55, 134-140

REFERENCE   1:  129:66847

L16  ANSWER 7 OF 30  REGISTRY  COPYRIGHT 1999 ACS
RN   208204-51-7  REGISTRY
CN   Interleukin 18 [38-serine,68-serine,76-alanine] (human) (9CI)  (CA INDEX
     NAME)
SQL  157
RN   208204-51-7  REGISTRY

SEQ       1 YFGKLESKLS VIRNLNDQVL FIDQGNRPLF EDMTDSDSRD NAPRTIFIIS
                           ===== =         = =====
         51 MYKDSQPRGM AVTISVKSEK ISTLSAENKI ISFKEMNPPD NIKDTKSDII
            =====
        101 FFQRSVPGHD NKMQFESSSY EGYFLACEKE RDLFKLILKK EDELGDRSIM
                                              =======
HITS AT:   16-21, 30-35, 51-55, 134-140

REFERENCE   1:  129:66847

L16  ANSWER 8 OF 30  REGISTRY  COPYRIGHT 1999 ACS
RN   208204-50-6  REGISTRY
CN   Interleukin 18 [38-serine,68-serine,76-serine,127-serine] (human) (9CI)
     (CA INDEX NAME)
SQL  157
RN   208204-50-6  REGISTRY

SEQ       1 YFGKLESKLS VIRNLNDQVL FIDQGNRPLF EDMTDSDSRD NAPRTIFIIS
                           ===== =         = =====
         51 MYKDSQPRGM AVTISVKSEK ISTLSSENKI ISFKEMNPPD NIKDTKSDII
            =====
        101 FFQRSVPGHD NKMQFESSSY EGYFLASEKE RDLFKLILKK EDELGDRSIM
                                              =======
HITS AT:   16-21, 30-35, 51-55, 134-140

REFERENCE   1:  129:66847

L16  ANSWER 9 OF 30  REGISTRY  COPYRIGHT 1999 ACS
RN   208204-49-3  REGISTRY
CN   Interleukin 18 [38-serine,68-serine,127-serine] (human) (9CI)  (CA INDEX
     NAME)
SQL  157
RN   208204-49-3  REGISTRY

SEQ       1 YFGKLESKLS VIRNLNDQVL FIDQGNRPLF EDMTDSDSRD NAPRTIFIIS
                           ===== =         = =====
         51 MYKDSQPRGM AVTISVKSEK ISTLSCENKI ISFKEMNPPD NIKDTKSDII
            =====                 =====
        101 FFQRSVPGHD NKMQFESSSY EGYFLASEKE RDLFKLILKK EDELGDRSIM
                                              =======
HITS AT:   16-21, 30-35, 51-55, 72-76, 134-140
```

```
REFERENCE   1:  129:66847

L16  ANSWER 10 OF 30  REGISTRY  COPYRIGHT 1999 ACS
RN   208204-48-2  REGISTRY
CN   Interleukin 18 [68-serine,127-serine] (human) (9CI)  (CA INDEX NAME)
SQL  157
RN   208204-48-2  REGISTRY

SEQ      1 YFGKLESKLS VIRNLNDQVL FIDQGNRPLF EDMTDSDCRD NAPRTIFIIS
                           ===== =        = =====
        51 MYKDSQPRGM AVTISVKSEK ISTLSCENKI ISFKEMNPPD NIKDTKSDII
           =====                  =====
       101 FFQRSVPGHD NKMQFESSSY EGYFLASEKE RDLFKLILKK EDELGDRSIM
                                               =======
HITS AT:   16-21, 30-35, 51-55, 72-76, 134-140

REFERENCE   1:  129:66847

L16  ANSWER 11 OF 30  REGISTRY  COPYRIGHT 1999 ACS
RN   208204-47-1  REGISTRY
CN   Interleukin 18 [38-serine,68-serine] (human) (9CI)  (CA INDEX NAME)
SQL  157
RN   208204-47-1  REGISTRY

SEQ      1 YFGKLESKLS VIRNLNDQVL FIDQGNRPLF EDMTDSDSRD NAPRTIFIIS
                           ===== =        = =====
        51 MYKDSQPRGM AVTISVKSEK ISTLSCENKI ISFKEMNPPD NIKDTKSDII
           =====                  =====
       101 FFQRSVPGHD NKMQFESSSY EGYFLACEKE RDLFKLILKK EDELGDRSIM
                                               =======
HITS AT:   16-21, 30-35, 51-55, 72-76, 134-140

REFERENCE   1:  129:66847

L16  ANSWER 12 OF 30  REGISTRY  COPYRIGHT 1999 ACS
RN   208204-46-0  REGISTRY
CN   Interleukin 18 [68-serine] (human) (9CI)  (CA INDEX NAME)
SQL  157
RN   208204-46-0  REGISTRY

SEQ      1 YFGKLESKLS VIRNLNDQVL FIDQGNRPLF EDMTDSDCRD NAPRTIFIIS
                           ===== =        = =====
        51 MYKDSQPRGM AVTISVKSEK ISTLSCENKI ISFKEMNPPD NIKDTKSDII
           =====                  =====
       101 FFQRSVPGHD NKMQFESSSY EGYFLACEKE RDLFKLILKK EDELGDRSIM
                                               =======
HITS AT:   16-21, 30-35, 51-55, 72-76, 134-140

REFERENCE   1:  129:66847

L16  ANSWER 13 OF 30  REGISTRY  COPYRIGHT 1999 ACS
RN   208197-35-7  REGISTRY
CN   Interleukin 18 (mouse) (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   Interleukin 18 [70-methionine] (mouse)
SQL  157
RN   208197-35-7  REGISTRY

SEQ      1 NFGRLHCTTA VIRNINDQVL FVDKRQPVFE DMTDIDQSAS EPQTRLIIYM
                           ===== =       == ====                =
        51 YKDSEVRGLA VTLSVKDSKM STLSCKNKII SFEEMDPPEN IDDIQSDLIF
           ====                  =====
       101 FQRRVPGHNK MEFESSLYEG HFLACQKEDD AFKLILKKKD ENGDKSVMFT
                                             =======
HITS AT:   16-21, 29-34, 50-54, 71-75, 132-138
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REFERENCE   1:  129:215727

REFERENCE   2:  129:108017

REFERENCE   3:  129:66847

L16  ANSWER 14 OF 30  REGISTRY  COPYRIGHT 1999 ACS
RN   208125-72-8  REGISTRY
CN   L-Serine, L-methionyl-L-tyrosyl-L-lysyl-L-.alpha.-aspartyl- (9CI)  (CA
     INDEX NAME)
SQL  5
RN   208125-72-8  REGISTRY

SEQ       1 MYKDS
            =====
HITS AT:    1-5

REFERENCE   1:  129:66847

L16  ANSWER 15 OF 30  REGISTRY  COPYRIGHT 1999 ACS
RN   208125-71-7  REGISTRY
CN   L-Aspartic acid, L-phenylalanyl-L-.alpha.-glutamyl-L-.alpha.-aspartyl-L-
     methionyl-L-threonyl- (9CI)  (CA INDEX NAME)
SQL  6
RN   208125-71-7  REGISTRY

SEQ       1 FEDMTD
            ======
HITS AT:    1-6

REFERENCE   1:  129:215727

REFERENCE   2:  129:66847

L16  ANSWER 16 OF 30  REGISTRY  COPYRIGHT 1999 ACS
RN   208125-70-6  REGISTRY
CN   L-Phenylalanine, L-asparaginyl-L-.alpha.-aspartyl-L-glutaminyl-L-valyl-L-
     leucyl- (9CI)  (CA INDEX NAME)
SQL  6
RN   208125-70-6  REGISTRY

SEQ       1 NDQVLF
            ======
HITS AT:    1-6

REFERENCE   1:  129:215727

REFERENCE   2:  129:66847

L16  ANSWER 17 OF 30  REGISTRY  COPYRIGHT 1999 ACS
RN   202608-43-3  REGISTRY
CN   Proteinase, interleukin 1.beta. precursor [73-isoleucine] (human clone
     pRCHuGF precursor) (9CI)  (CA INDEX NAME)
SQL  193
RN   202608-43-3  REGISTRY

SEQ      51 LNDQVLFIDQ GNRPLFEDMT DSDCRDNAPR TIFIISMYKD SQPRGMAVTI
             ======          ===== =                ==== =
        151 FESSSYEGYF LACEKERDLF KLILKKEDEL GDRSIMFTVQ NED
                               = ======
HITS AT:    52-57, 66-71, 87-91, 170-176

REFERENCE   1:  128:166370

REFERENCE   2:  128:151108
```

```
L16  ANSWER 18 OF 30  REGISTRY  COPYRIGHT 1999 ACS
RN   193294-41-6  REGISTRY
CN   Interferon .gamma.-inducing factor-2 (human large isoform) (9CI)  (CA
     INDEX NAME)
SQL  205
RN   193294-41-6  REGISTRY

SEQ      51 LNDQVLFIDQ GNRPLFEDMT DSDCRDNAPR TIFIISMYKD SQPRGMAVTI
              ======          ===== =                ==== =
        101 SVKCEKISTL SCENKIISFK EMNPPDNIKD TKSDIIFFQR SVPGHDNKMQ
                   === ==
        151 FESSSYEGYF LACEKERDLF KLILKKEDEL GDRSIMFTVQ NEDGKVEMNL
                                = ======
HITS AT:   52-57, 66-71, 87-91, 108-112, 170-176

REFERENCE   1:  127:148345

L16  ANSWER 19 OF 30  REGISTRY  COPYRIGHT 1999 ACS
RN   193294-40-5  REGISTRY
CN   Interferon .gamma.-inducing factor-2 [140-arginine] (human short isoform)
     (9CI)  (CA INDEX NAME)
SQL  193
RN   193294-40-5  REGISTRY

SEQ      51 LNDQVLFIDQ GNRPLFEDMT DSDCRDNAPR TIFIISMYKD SQPRGMAVTI
              ======          ===== =                ==== =
        101 SVKCEKISTL SCENKIISFK EMNPPDNIKD TKSDIIFFQI SVPGHDNKMQ
                   === ==
        151 FESSSYEGYF LACEKERDLF KLILKKEDEL GDRSIMFTVQ NED
                                = ======
HITS AT:   52-57, 66-71, 87-91, 108-112, 170-176

REFERENCE   1:  127:148345

L16  ANSWER 20 OF 30  REGISTRY  COPYRIGHT 1999 ACS
RN   189326-26-9  REGISTRY
CN   L-Serine, L-tyrosyl-L-phenylalanylglycyl-L-lysyl-L-leucyl-L-.alpha.-
     glutamyl-L-seryl-L-lysyl-L-leucyl-L-seryl-L-valyl-L-isoleucyl-L-arginyl-L-
     asparaginyl-L-leucyl-L-asparaginyl-L-.alpha.-aspartyl-L-glutaminyl-L-valyl-
     L-leucyl-L-phenylalanyl-L-isoleucyl-L-.alpha.-aspartyl-L-glutaminylglycyl-
     L-asparaginyl-L-arginyl-L-prolyl-L-leucyl-L-phenylalanyl-L-.alpha.-
     glutamyl-L-.alpha.-aspartyl-L-methionyl-L-threonyl-L-.alpha.-aspartyl-L-
     seryl-L-.alpha.-aspartyl-L-cysteinyl-L-arginyl-L-.alpha.-aspartyl-L-
     asparaginyl-L-alanyl-L-prolyl-L-arginyl-L-threonyl-L-isoleucyl-L-
     phenylalanyl-L-isoleucyl-L-isoleucyl- (9CI)  (CA INDEX NAME)
SQL  50
RN   189326-26-9  REGISTRY

SEQ       1 YFGKLESKLS VIRNLNDQVL FIDQGNRPLF EDMTDSDCRD NAPRTIFIIS
                                ===== =          = =====
HITS AT:   16-21, 30-35

REFERENCE   1:  126:316334

L16  ANSWER 21 OF 30  REGISTRY  COPYRIGHT 1999 ACS
RN   189304-55-0  REGISTRY
CN   Interleukin 18 (human) (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   Protein [73-threonine] (human interferon .gamma.-inducing)
SQL  157
RN   189304-55-0  REGISTRY

SEQ       1 YFGKLESKLS VIRNLNDQVL FIDQGNRPLF EDMTDSDCRD NAPRTIFIIS
                                ===== =          = =====
         51 MYKDSQPRGM AVTISVKCEK ISTLSCENKI ISFKEMNPPD NIKDTKSDII
```

```
        =====                 =====
   101 FFQRSVPGHD NKMQFESSSY EGYFLACEKE RDLFKLILKK EDELGDRSIM
                                           =======
HITS AT:   16-21, 30-35, 51-55, 72-76, 134-140

REFERENCE   1:  129:215727

REFERENCE   2:  129:66847

REFERENCE   3:  128:166370

REFERENCE   4:  128:151108

REFERENCE   5:  128:137190

REFERENCE   6:  126:316334
```

```
L16  ANSWER 22 OF 30  REGISTRY  COPYRIGHT 1999 ACS
RN   189304-54-9  REGISTRY
CN   Protein [73-isoleucine] (human interferon .gamma.-inducing) (9CI)  (CA
     INDEX NAME)
OTHER NAMES:
CN   Interleukin 18 [73-isoleucine] (human)
CN   Proteinase, interleukin 1.beta. precursor [73-isoleucine] (human clone
     pCDHICE)
SQL  157
RN   189304-54-9  REGISTRY

SEQ      1 YFGKLESKLS VIRNLNDQVL FIDQGNRPLF EDMTDSDCRD NAPRTIFIIS
                           ===== =        = =====
        51 MYKDSQPRGM AVTISVKCEK ISILSCENKI ISFKEMNPPD NIKDTKSDII
           =====
       101 FFQRSVPGHD NKMQFESSSY EGYFLACEKE RDLFKLILKK EDELGDRSIM
                                              =======
HITS AT:   16-21, 30-35, 51-55, 134-140

REFERENCE   1:  129:108017

REFERENCE   2:  128:166370

REFERENCE   3:  128:151108

REFERENCE   4:  128:137190

REFERENCE   5:  126:316334
```

```
L16  ANSWER 23 OF 30  REGISTRY  COPYRIGHT 1999 ACS
RN   189265-23-4  REGISTRY
CN   L-Arginine, L-threonyl-L-isoleucyl-L-phenylalanyl-L-isoleucyl-L-isoleucyl-
     L-seryl-L-methionyl-L-tyrosyl-L-lysyl-L-.alpha.-aspartyl-L-seryl-L-
     glutaminyl-L-prolyl- (9CI)  (CA INDEX NAME)
SQL  14
RN   189265-23-4  REGISTRY

SEQ      1 TIFIISMYKD SQPR
                 ==== =
HITS AT:   7-11

REFERENCE   1:  128:320553

REFERENCE   2:  126:316334
```

```
L16  ANSWER 24 OF 30  REGISTRY  COPYRIGHT 1999 ACS
RN   186847-62-1  REGISTRY
CN   Interferon .gamma.-inducing factor (Rattus norvegicus strain
     Sprague-Dawley adrenal gland gene IGIF isoform .alpha. precursor) (9CI)
```

(CA INDEX NAME)
OTHER NAMES:
CN GenBank U77777-derived protein GI 1809131
CN Interleukin 1.gamma. (Rattus norvegicus strain Sprague-Dawley adrenal gland gene IGIF isoform .alpha. precursor)
CN Interleukin 18 (Rattus norvegicus strain Sprague-Dawley adrenal gland gene IGIF isoform .alpha. precursor)
SQL 175
RN **186847-62-1** REGISTRY

```
SEQ      51 INDQVLFVDK RNPPVFEDMP DIDRTANESQ TRLIIYMYKD SEVRGLAVTL
               ======                                ==== =
        101 SVKDGRMSTL SCKNKIISFE KRVPGHNKME FESSLYEGHF LACQKEDDAF
                      === ==
```
HITS AT: 52-57, 87-91, 108-112

REFERENCE 1: 128:229370

REFERENCE 2: 126:156262

L16 ANSWER 25 OF 30 REGISTRY COPYRIGHT 1999 ACS
RN **186847-61-0** REGISTRY
CN Interferon .gamma.-inducing factor (Rattus norvegicus strain Sprague-Dawley adrenal gland gene IGIF precursor) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN GenBank U77776-derived protein GI 1809129
CN Interleukin 1.gamma. (Rattus norvegicus strain Sprague-Dawley adrenal gland gene IGIF precursor)
CN Interleukin 18 (Rattus norvegicus strain Sprague-Dawley adrenal gland gene IGIF precursor)
SQL 194
RN **186847-61-0** REGISTRY

```
SEQ      51 INDQVLFVDK RNPPVFEDMP DIDRTANESQ TRLIIYMYKD SEVRGLAVTL
               ======                                ==== =
        101 SVKDGRMSTL SCKNKIISFE EMNPPENIDD IKSDLIFFQK RVPGHNKMEF
                      === ==
```
HITS AT: 52-57, 87-91, 108-112

REFERENCE 1: 128:229370

REFERENCE 2: 126:156262

L16 ANSWER 26 OF 30 REGISTRY COPYRIGHT 1999 ACS
RN **178254-43-8** REGISTRY
CN Protein (human clone pHIGIF interferon .gamma.-inducing precursor) (9CI) (CA INDEX NAME)
NTE

type	------ location ------	description
uncommon	Aaa-109 - -	

SQL 193
RN **178254-43-8** REGISTRY

```
SEQ      51 LNDQVLFIDQ GNRPLFEDMT DSDCRDNAPR TIFIISMYKD SQPRGMAVTI
               ======      ===== =               ==== =
        151 FESSSYEGYF LACEKERDLF KLILKKEDEL GDRSIMFTVQ NED
                                 = ======
```
HITS AT: 52-57, 66-71, 87-91, 170-176

REFERENCE 1: 128:137190

REFERENCE 2: 125:84660

```
L16  ANSWER 27 OF 30  REGISTRY  COPYRIGHT 1999 ACS
RN   178254-42-7  REGISTRY
CN   Protein (human clone pHIGIF interferon .gamma.-inducing) (9CI)  (CA INDEX
     NAME)
NTE
-------------------------------------------------------------------------
 type            ------ location ------          description
-------------------------------------------------------------------------
uncommon         Aaa-73          -          -
-------------------------------------------------------------------------
SQL  157
RN   178254-42-7  REGISTRY

SEQ      1 YFGKLESKLS VIRNLNDQVL FIDQGNRPLF EDMTDSDCRD NAPRTIFIIS
                           ===== =         = =====
        51 MYKDSQPRGM AVTISVKCEK ISXLSCENKI ISFKEMNPPD NIKDTKSDII
           =====
       101 FFQRSVPGHD NKMQFESSSY EGYFLACEKE RDLFKLILKK EDELGDRSIM
                                               =======
HITS AT:   16-21, 30-35, 51-55, 134-140

REFERENCE   1:  128:137190

REFERENCE   2:  125:84660

L16  ANSWER 28 OF 30  REGISTRY  COPYRIGHT 1999 ACS
RN   178234-94-1  REGISTRY
CN   Interleukin 18 (human precursor) (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   Cytokine IGIF (human precursor)
CN   Interferon .gamma.-inducing factor (human precursor)
CN   Interferon .gamma.-inducing factor-2 (human short isoform precursor)
CN   Interleukin 18 (human monocyte precursor)
SQL  193
RN   178234-94-1  REGISTRY

SEQ     51 LNDQVLFIDQ GNRPLFEDMT DSDCRDNAPR TIFIISMYKD SQPRGMAVTI
            ======         ===== =          ==== =
       101 SVKCEKISTL SCENKIISFK EMNPPDNIKD TKSDIIFFQR SVPGHDNKMQ
                  === ==
       151 FESSSYEGYF LACEKERDLF KLILKKEDEL GDRSIMFTVQ NED
                              = ======
HITS AT:   52-57, 66-71, 87-91, 108-112, 170-176

REFERENCE   1:  128:166370

REFERENCE   2:  128:151108

REFERENCE   3:  128:58316

REFERENCE   4:  127:357917

REFERENCE   5:  127:148345

REFERENCE   6:  125:55848

L16  ANSWER 29 OF 30  REGISTRY  COPYRIGHT 1999 ACS
RN   174066-57-0  REGISTRY
CN   Protein (mouse clone pKGFM5 interferon .gamma.-inducing) (9CI)  (CA INDEX
     NAME)
OTHER NAMES:
CN   Protein (mouse interferon .gamma.-inducing)
NTE
-------------------------------------------------------------------------
 type            ------ location ------          description
-------------------------------------------------------------------------
```

```
uncommon         Aaa-70           -          -
----------------------------------------------------------------------------
```

SQL 157
RN **174066-57-0** REGISTRY

```
SEQ      1 NFGRLHCTTA VIRNINDQVL FVDKRQPVFE DMTDIDQSAS EPQTRLIIYM
                           ===== =       == ====                =
        51 YKDSEVRGLA VTLSVKDSKX STLSCKNKII SFEEMDPPEN IDDIQSDLIF
           ====                  =====
       101 FQKRVPGHNK MEFESSLYEG HFLACQKEDD AFKLILKKKD ENGDKSVMFT
                                             =======
HITS AT:   16-21, 29-34, 50-54, 71-75, 132-138
```

REFERENCE 1: 125:84660

REFERENCE 2: 124:173455

L16 ANSWER 30 OF 30 REGISTRY COPYRIGHT 1999 ACS
RN **171041-98-8** REGISTRY
CN Cytokine IGIF (Mus musculus clone pMuGF37B-5 interferon .gamma.-inducing factor precursor) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Interferon .gamma.-inducing factor (Mus musculus clone pMuGF37B-5 precursor)
SQL 192
RN **171041-98-8** REGISTRY

```
SEQ     51 NDQVLFVDKR QPVFEDMTDI DQSASEPQTR LIIYMYKDSE VRGLAVTLSV
           ======        ======                ===== 
       101 KDSKMSTLSC KNKIISFEEM DPPENIDDIQ SDLIFFQKRV PGHNKMEFES
                =====
       151 SLYEGHFLAC QKEDDAFKLI LKKKDENGDK SVMFTLTNLH QS
                        ==== ===
HITS AT:   51-56, 64-69, 85-89, 106-110, 167-173
```

REFERENCE 1: 124:6762

EP 861663 A2 19980902 EP 98-301352 19980224
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO
JP 10236974 A2 19980908 JP 97-55468 19970225
PRIORITY APPLN. INFO.: JP 97-55468 19970225

AB An **osteoclastigenesis**-inhibitory agent which comprises an **interleukin-18** and/or its functional equiv. is disclosed. The agent can be arbitrarily used as an ingredient for cell culture and agents for regulating bone resorption and for **osteoclast**-related diseases, directed to treat and/or prevent hypercalcemia, **osteoclastoma**, osteoporosis, etc.

IT **189304-55-0, Interleukin 18** (human)
208197-35-7, Interleukin 18 (mouse)
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(amino acid sequence; **osteoclastigenesis**-inhibitory agent comprising **interleukin-18**)

L5 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1998:566420 HCAPLUS
DOCUMENT NUMBER: 129:314628
TITLE: Interleukins in the control of **osteoclast** differentiation
AUTHOR(S): Martin, T. J.; Romas, E.; Gillespie, M. T.
CORPORATE SOURCE: St. Vincent's Institute of Medical Research, Fitzroy, Victoria, 3065, Australia
SOURCE: Crit. Rev. Eukaryotic Gene Expression (1998), 8(2), 107-123
CODEN: CFGEEJ; ISSN: 1045-4403
PUBLISHER: Begell House, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with approx. 140 refs. To maintain homeostasis of bone, the prodn. of osteoblasts and **osteoclasts** is tightly regulated. At the local level, hormones and cytokines control formation of **osteoclasts** from hemopoietic precursors by acting upon osteoblastic-stromal cells and in some cases also upon cells of the immune system. Osteoblasts regulate **osteoclast** formation by providing phys. support and cytokines such as M-CSF and IL-11, which promote **osteoclast** differentiation. Osteoblasts are also a source of **IL-18**, which limits **osteoclast** formation. The requirement of contact between osteoblasts and hemopoietic cells for successful **osteoclast** formation led to a concept of a membrane-anchored stromal cell mol. that programs **osteoclast** differentiation. This mechanism has been highlighted by the discovery of osteoprotegerin (OPG), a sol. tumor necrosis factor (TNF) family member that inhibits **osteoclast** formation. The ligand for OPG is a novel transmembrane TNF receptor superfamily member, the **osteoclast** differentiating factor (ODF).

L5 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1998:84241 HCAPLUS
DOCUMENT NUMBER: 128:191446
TITLE: **Interleukin 18** inhibits **osteoclast** formation via T cell production of granulocyte macrophage colony-stimulating factor
AUTHOR(S): Horwood, Nicole J.; Udagawa, Nobuyuki; Elliott, Jan; Grail, Dianne; Okamura, Haruki; Kurimoto, Masashi; Dunn, Ashley R.; Martin, T. John; Gillespie, Matthew T.
CORPORATE SOURCE: St. Vincent's Institute of Medical Research and The University of Melbourne, Department of Medicine, St. Vincent's Hospital, Fitzroy, 3065, Australia
SOURCE: J. Clin. Invest. (1998), 101(3), 595-603
CODEN: JCINAO; ISSN: 0021-9738

show files
File 5:Biosis Previews(R) 1969-1999/Jun W3
(c) 1999 BIOSIS
File 15:ABI/INFORM(R) 1971-1999/Jun 23
(c) 1999 UMI
File 34:SciSearch(R) Cited Ref Sci 1990-1999/Jun W3
(c) 1999 Inst for Sci Info
File 47:Magazine Database(TM) 1959-1999/Jun 23
(c) 1999 The Gale group
File 71:ELSEVIER BIOBASE 1994-1999/Apr W2
(c) 1999 Elsevier Science B.V.
File 73:EMBASE 1974-1999/Jun W1
(c) 1999 Elsevier Science B.V.
File 76:Life Sciences Collection 1982-1999/Apr
(c) 1999 Cambridge Sci Abs
File 94:JICST-EPlus 1985-1999/Feb W4
(c)1999 Japan Science and Tech Corp(JST)
File 155:MEDLINE(R) 1966-1999/Aug W2
(c) format only 1999 Dialog Corporation
File 172:EMBASE Alert 1999/Jun W1
(c) 1999 Elsevier Science B.V.
File 351:DERWENT WPI 1963-1999/UD=9923;UP=9923;UM=9923
(c)1999 Derwent Info Ltd
File 370:Science 1996-1999/May W1
(c) 1999 AAAS
File 440:Current Contents Search(R) 1990-1999/Jul W1
(c) 1999 Inst for Sci Info
?
?
?ds s1-s2

Set	Items	Description
S1	1450	((IL OR INTERLEUKIN)(W)18 OR INTERFERON(W)GAMMA(W)INDUCING-(W)FACTOR? OR IGIF?)
S2	30	S1 AND OSTEOCLAST?

?
?
? s2/7/1-30

2/7/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11738882 BIOSIS NO.: 199800519578
Interleukin-*18*: Perspectives on the newest interleukin.

AUTHOR: Gillespie Matthew T(a); Horwood Nicole J
AUTHOR ADDRESS: (a)St. Vincent's Inst. Med. Res. Univ. Melbourne, Dep. Med., St. Vincent's Hosp., Fitzroy, VIC 3065, Australia

JOURNAL: Cytokine & Growth Factor Reviews 9 (2):p109-116 June, 1998
ISSN: 1359-6101
DOCUMENT TYPE: Literature Review
RECORD TYPE: Citation
LANGUAGE: English

2/7/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11674818 BIOSIS NO.: 199800456549
Interleukins in the control of *osteoclast* differentiation.

AUTHOR: Martin T J; Romas E; Gillespie M T
AUTHOR ADDRESS: St. Vincent's Inst. Med. Res., 9 Princes Street, Fitzroy 3065, Victoria, Australia

JOURNAL: Critical Reviews in Eukaryotic Gene Expression 8 (2):p107-123 1998
ISSN: 1045-4403
DOCUMENT TYPE: Literature Review
RECORD TYPE: Citation
LANGUAGE: English

2/7/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11349845 BIOSIS NO.: 199800131177
Interleukin *18* inhibits *osteoclast* formation via T cell production of granulocyte macrophage colony-stimulating factor.

AUTHOR: Horwood Nicole J; Udagawa Nobuyuki; Elliott Jan; Grail Dianne; Okamura Haruki; Kurimoto Masashi; Dunn Ashley R; Martin T John; Gillespie Matthew T(a)
AUTHOR ADDRESS: (a)St. Vincent's Inst. Med. Res., 41 Victoria Parade, Fitzroy, VIC 3065, Australia

JOURNAL: Journal of Clinical Investigation 101 (3):p595-603 Feb. 1, 1998
ISSN: 0021-9738
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: *IL*-*18* inhibits *osteoclast* (OCL) formation in vitro independent of IFN-gamma production, and this was abolished by the addition of neutralizing antibodies to GM-CSF. We now establish that *IL* -*18* was unable to inhibit OCL formation in cocultures using GM-CSF-deficient mice (GM-CSF -/-). Reciprocal cocultures using either wild-type osteoblasts with GM-CSF -/- spleen cells or GM-CSF -/- osteoblasts with wild-type spleen cells were examined. Wild-type spleen cells were required to elicit a response to *IL*-*18* indicating that cells of splenic origin were the *IL*-*18* target. As T cells comprise a large proportion of the spleen cell population, the role of T cells in *osteoclastogenesis* was examined. Total T cells were removed and repleted in various combinations. Addition of wild-type T cells to a GM-CSF -/- coculture restored *IL*-*18* inhibition of *osteoclastogenesis*. Major subsets of T cells, CD4+ and CD8+, were also individually depleted. Addition of either CD4+ or CD8+ wild-type T cells restored *IL*-*18* action in a GM-CSF -/- background, while *IL*-*18* was ineffective when either CD4+ or CD8+ GM-CSF -/- T cells were added to a wild-type coculture. These results highlight the involvement of T cells in *IL*-*18*-induced OCL inhibition and provide evidence for a new OCL inhibitory pathway whereby *IL*-*18* inhibits OCL formation due to action upon T cells promoting the release of GM-CSF, which in turn acts upon OCL recursors.

2/7/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10882805 BIOSIS NO.: 199799503950
Interleukin-*18* (*interferon*-*gamma*-*inducing* *factor*) is produced by osteoblasts and acts via granulocyte/macrophage colony-stimulating factor and not via interferon-gamma to inhibit *osteoclast* formation.

AUTHOR: Udagawa Nobuyuki; Horwood Nicole J; Elliot Jan; Mackay Alan; Owens Jane; Okamura Haruki; Kurimoto Masashi; Chambers Timothy J; Martin T John ; Gillespie Matthew T(a)
AUTHOR ADDRESS: (a)St. Vincent's Inst. Medical Research, 41 Victoria Parade, Fitzroy 3065, Vic, Australia

JOURNAL: Journal of Experimental Medicine 185 (6):p1005-1012 1997
ISSN: 0022-1007
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We have established by differential display polymerase chain reaction of mRNA that interleukin (*IL*)-*18* is expressed by osteoblastic stromal cells. The stromal cell populations used for comparison differed in their ability to promote *osteoclast*-like multinucleated cell (OCL) formation. mRNA for *IL*-*18* was found to be expressed in greater abundance in lines that were unable to support OCL formation than in supportive cells. Recombinant *IL*-*18* was found to inhibit OCL formation in cocultures of osteoblasts and hemopoietic cells of spleen or bone marrow origin. *IL*-*18* inhibited OCL formation in the presence of *osteoclastogenic* agents including 1-alpha,25-dihydroxyvitamin D-3, prostaglandin E-2, parathyroid hormone, IL- 1, and IL-11. The inhibitory effect of *IL*-*18* was limited to the early phase of the cocultures, which coincides with proliferation of hemopoietic precursors. *IL*-*18* has been reported to induce interferon-gamma (IFN-gamma) and granulocyte/macrophage colony-stimulating factor (GM-CSF) production in T cells, and both agents also inhibit OCL formation in vitro. Neutralizing antibodies to GM-CSF were able to rescue *IL*-*18* inhibition of OCL formation, whereas neutralizing antibodies to IFN-gamma did not. In cocultures with osteoblasts and spleen cells from IFN-gamma receptor type II-deficient mice, *IL*-*18* was found to inhibit OCL formation, indicating that *IL*-*18* acted independently of IFN-gamma production: IFN-gamma had no effect in these cocultures. Additionally, in cocultures in which spleen cells were derived from receptor-deficient mice and osteoblasts were from wild-type mice and vice versa, we identified that the target cells for IFN-gamma inhibition of OCL formation were the hemopoietic cells. The work provides evidence that *IL*-*18* is expressed by osteoblasts and inhibits OCL formation via GM-CSF production and not via IFN-gamma production.

2/7/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

06254127 BIOSIS NO.: 000086088310
TRANSFORMING GROWTH FACTOR BETA INHIBITS BONE RESORPTION IN FETAL RAT LONG BONE CULTURES

AUTHOR: PFEILSCHIFTER J; SEYEDIN S M; MUNDY G R

AUTHOR ADDRESS: DIV. ENDOCRINOL. AND METABOLISM, UNIV. TEXAS HEALTH SCI. CENT. SAN ANTONIO, 7703 FLOYD CURL DRIVE, SAN ANTONIO, TEX. 78284-7877.

JOURNAL: J CLIN INVEST 82 (2). 1988. 680-685.
FULL JOURNAL NAME: Journal of Clinical Investigation
CODEN: JCINA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: TGF-.beta.1 is a polypeptide that is abundant in bone matrix, is produced by bone cells, and modulates proliferation and differentiated functions of osteoblastic cells in vitro. TGF-.beta.2 is a closely related polypeptide that was originally isolated from bone matrix. TGF-.beta.1 has been shown previously to stimulate prostaglandin production in cultures of neonatal mouse calvariae, which causes these bones to resorb. We found similar effects with TGF-.beta.2. In comparison, TGF-.beta.1 and TGF-.beta.2 failed to stimulate bone resorption in fetal rat long bone cultures during a 3-d incubation period in concentrations up to 50-100 times greater than those capable of inducing bone resorption in calvariae. Incubation with TGF-.beta.1 for a further 3 d decreased bone resorption up to 30%. Moreover, bone resorption induced by the bone-resorbing agents IL 1 and 1,25-dihyroxyvitamin D3 was partially or completely inhibited by TGF-.beta.1 and TGF-.beta.2 during the second half of the 6-d incubation period. Inhibition of DNA synthesis with hydroxyurea inhibited bone resorption in long bones in a similar pattern to that seen with TGF-.beta.1. The inhibitory effects of TGF-.beta.1 and TGF-.beta.2 on bone resorption in long bone cultures may therefore be due to inhibition of *osteoclast* precursor proliferation.

2/7/6 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

06971963 Genuine Article#: 110EV Number of References: 143
Title: Interleukins in the control of *osteoclast* differentiation
Author(s): Martin TJ; Romas E; Gillespie MT
Corporate Source: ST VINCENTS INST MED RES,/FITZROY/VIC 3065/AUSTRALIA/
Journal: CRITICAL REVIEWS IN EUKARYOTIC GENE EXPRESSION, 1998, V8, N2, P 107-123
ISSN: 1045-4403 Publication date: 19980000
Publisher: BEGELL HOUSE INC, 79 MADISON AVE, SUITE 1205, NEW YORK, NY 10016-7892
Language: English Document Type: REVIEW
Abstract: To maintain homeostasis of bone, the production of osteoblasts and *osteoclasts* is tightly regulated. At the local level, hormones and cytokines control formation of *osteoclasts* from hemopoietic precursors by acting upon osteoblastic-stromal cells and in some cases also upon cells of the immune system. Osteoblasts regulate *osteoclast* formation by providing physical support and cytokines such as M-CSF and IL-11, which promote *osteoclast* differentiation. Osteoblasts are also a source of *IL*-*18*, which limits *osteoclast* formation. The require ment of contact between osteoblasts and hemopoietic cells for successful *osteoclast* formation led to a concept of a membrane-anchored stromal cell molecule that programs *osteoclast* differentiation. This mechanism has been highlighted by the discovery of osteoprotegerin (OPG), a soluble tumor necrosis factor (TNF) family member that inhibits *osteoclast* formation. The ligand for OPG is a novel transmembrane TNF receptor superfamily member, the *osteoclast*

differentiating factor (ODF). The recognition of the osteoprotegerin/osteoprotegerin-ligand axis will lead to new insights into the control of *osteoclast* differentiation by interleukins.

2/7/7 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

06480038 Genuine Article#: YW195 Number of References: 25
Title: *Interleukin* *18* inhibits *osteoclast* formation via T cell production of granulocyte macrophage colony-stimulating factor
Author(s): Horwood NJ; Udagawa N; Elliott J; Grail D; Okamura H; Kurimoto M ; Dunn AR; Martin TJ; Gillespie MT (REPRINT)
Corporate Source: ST VINCENTS INST MED RES,41 VICTORIA PARADE/FITZROY/VIC 3065/AUSTRALIA/ (REPRINT); ST VINCENTS INST MED RES,/FITZROY/VIC 3065/AUSTRALIA/; UNIV MELBOURNE,ST VINCENTS HOSP, DEPT MED/FITZROY/VIC 3065/AUSTRALIA/; SHOWA UNIV,SCH DENT, DEPT BIOCHEM/TOKYO 142//JAPAN/; LUDWIG INST CANC RES,/PARKVILLE/VIC 3052/AUSTRALIA/; HYOGO MED UNIV,DEPT IMMUNOL & MED ZOOL/NISHINOMIYA/HYOGO 663/JAPAN/; HAYASHIBARA BIOCHEM LABS INC,FUJISAKI INST/OKAYAMA 702//JAPAN/
Journal: JOURNAL OF CLINICAL INVESTIGATION, 1998, V101, N3 (FEB 1), P 595-603
ISSN: 0021-9738 Publication date: 19980201
Publisher: ROCKEFELLER UNIV PRESS, 1114 FIRST AVE, 4TH FL, NEW YORK, NY 10021
Language: English Document Type: ARTICLE
Abstract: *IL*-*18* inhibits *osteoclast* (OCL) formation in vitro independent of IFN-gamma production, and this was abolished by the addition of neutralizing antibodies to GM-CSF, We now establish that *IL*-*18* was unable to inhibit OCL formation in cocultures using GM-CSF-deficient mice (GM-CSF -/-). Reciprocal cocultures using either wild-type osteoblasts with GM-CSF -/- spleen cells or GM-CSF -/- osteoblasts with wild-type spleen cells were examined. Wild-type spleen cells were required to elicit a response to *IL*-*18* indicating that cells of splenic origin were the *IL*-*18* target. As T cells comprise a large proportion of the spleen cell population, the role of T cells in *osteoclastogenesis* was examined. Total T cells were removed and repleted in various combinations, Addition of wild-type T cells to a GM-CSF -/- coculture restored *IL*-*18* inhibition of *osteoclastogenesis*, Major subsets of T cells, CD4(+) and CD8(+), were also individually depleted, Addition of either CD4(+) or CD8(+) wildtype T cells restored *IL*-*18* action in a GM-CSF -/- background, while *IL*-*18* was ineffective when either CD4(+) or CD8(+) GM-CSF -/- T cells were added to a wild-type coculture. These results highlight the involvement of T cells in *IL*-*18*-induced OCL inhibition and provide evidence for a new OCL inhibitory pathway whereby *IL*-*18* inhibits OCL formation due to action upon T cells promoting the release of GM-CSF, which in turn acts upon OCL precursors.

2/7/8 (Item 3 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

06104525 Genuine Article#: XP627 Number of References: 0
Title: *Interleukin*-*18* inhibits *osteoclast* formation via T-cell production of GM-CSF.
Author(s): Horwood NJ; Udagawa N; Elliott I; Okamura H; Kurimoto M; Dunn A; Chambers TJ; Martin TJ; Gillespie MT

Corporate Source: ST VINCENTS INST MED RES,/FITZROY/VIC 3065/AUSTRALIA/; HYOGO MED UNIV,DEPT BACTERIOL/NISHINOMIYA/HYOGO/JAPAN/; FUJISAKI INST,/OKAYAMA//JAPAN/; LUDWIG INST,/MELBOURNE/VIC/AUSTRALIA/; UNIV LONDON ST GEORGES HOSP,SCH MED, DEPT HISTOPATHOL/LONDON//ENGLAND/
Journal: JOURNAL OF BONE AND MINERAL RESEARCH, 1997, V12, 1 (AUG), P183-183
ISSN: 0884-0431 Publication date: 19970800
Publisher: BLACKWELL SCIENCE INC, 350 MAIN ST, MALDEN, MA 02148
Language: English Document Type: MEETING ABSTRACT

2/7/9 (Item 4 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

05672761 Genuine Article#: WP404 Number of References: 39
Title: *Interleukin*-*18* (*interferon*-*gamma*-*inducing* *factor*) is produced by osteoblasts and acts via granulocyte/macrophage colony-stimulating factor and not via interferon-gamma to inhibit *osteoclast* formation
Author(s): Udagawa N; Horwood NJ; Elliott J; Mackay A; Owens J; Okamura H; Kurimoto M; Chambers TJ; Martin TJ; Gillespie MT (REPRINT)
Corporate Source: ST VINCENTS INST MED RES,41 VICTORIA PARADE/FITZROY/VIC 3065/AUSTRALIA/ (REPRINT); ST VINCENTS INST MED RES,/FITZROY/VIC 3065/AUSTRALIA/; UNIV MELBOURNE,ST VINCENTS HOSP, DEPT MED/FITZROY/VIC 3065/AUSTRALIA/; ST GEORGE HOSP,SCH MED, DEPT HISTOPATHOL/LONDON SW17 0RE//ENGLAND/; HYOGO MED UNIV,DEPT BACTERIOL/NISHINOMIYA/HYOGO 663/JAPAN/; HAYASHIBARA BIOCHEM LABS INC,FUJISAKI INST/OKAYAMA 702//JAPAN/
Journal: JOURNAL OF EXPERIMENTAL MEDICINE, 1997, V185, N6 (MAR 17), P 1005-1012
ISSN: 0022-1007 Publication date: 19970317
Publisher: ROCKEFELLER UNIV PRESS, 1114 FIRST AVE, 4TH FL, NEW YORK, NY 10021
Language: English Document Type: ARTICLE
Abstract: We have established by differential display polymerase chain reaction of mRNA that interleukin (*IL*)-*18* is expressed by osteoblastic stromal cells. The stromal cell populations used for comparison differed in their ability to promote *osteoclast*-like multinucleated cell (OCL) formation. mRNA for *IL*-*18* was found to be expressed in greater abundance in lines that were unable to support OCL formation than in supportive cells. Recombinant *IL*-*18* was found to inhibit OCL formation in cocultures of osteoblasts and hemopoietic cells of spleen or bone marrow origin. *IL*-*18* inhibited OCL formation in the presence of *osteoclastogenic* agents including 1 alpha,25-dihydroxyvitamin D-3, prostaglandin E(2), parathyroid hormone, IL-1, and IL-11. The inhibitory effect of *IL*-*18* was limited to the early phase of the cocultures, which coincides with proliferation of hemopoietic precursors. *IL*-*18* has been reported to induce interferon-gamma (IFN-gamma) and granulocyte/macrophage colony-stimulating factor (GM-CSF) production in T cells, and both agents also inhibit OCL formation in vitro. Neutralizing antibodies to GM-CSF were able to rescue *IL*-*18* inhibition of OCL formation, whereas neutralizing antibodies to IFN-gamma did not. In cocultures with osteoblasts and spleen cells from IFN-gamma receptor type II-deficient mice, *IL*-*18* was found to inhibit OCL formation, indicating that *IL*-*18* acted independently of IFN-gamma production: IFN-gamma had no effect in these cocultures. Additionally, in cocultures in which spleen cells were derived from receptor-deficient mice and osteoblasts were from wild-type mice and vice versa, we identified that the target cells for IFN-gamma inhibition of OCL

formation were the hemopoietic cells. The work provides evidence that *IL*-*18* is expressed by osteoblasts and inhibits OCL formation via GM-CSF production and not via IFN-gamma production.

2/7/10 (Item 1 from file: 47)
DIALOG(R)File 47:Magazine Database(TM)

04689824 SUPPLIER NUMBER: 19061126 (THIS IS THE FULL TEXT)
Activation of *interferon*-*gamma* *inducing* *factor* mediated by interleukin-1 beta converting enzyme.
Gu, Yong; Kuida, Keisuke; Tsutsui, Hiroko; Ku, George; Hsiao, Kathy; Fleming, Mark A.; Hayashi, Nobuki; Higashino, Kazuya; Okamura, Haruki; Nakanishi, Kenji; Kurimoto, Masashi; Tanimoto, Tadao; Flavell, Richard A.; Sato, Vicki; Harding, Matthew; Livingston, David J.; Su, Michael S.-S.
Science, v275, n5297, p206(3)
Jan 10, 1997

TEXT:

ICE is a member of the growing family of ICE-like cysteine proteases (caspases) with a substrate specificity for aspartate (1). ICE (caspase-1) was identified on the basis of its proteolytic activity for cleaving the inactive IL-1(beta) precursor into the 17-kD mature cytokine (2). ICE-deficient mice are impaired in their production of mature IL-1(beta) (3), which establishes the physiological role of ICE in the processing and export of IL-1(beta). In contrast to IL-1(beta)-deficient mice (4), (ICE.sup.-/-) mice also have less IL-1(alpha), tumor necrosis factor-(alpha) (TNF-(alpha)), and IL-6 and are resistant to septic shock induced by endotoxin (3), which suggests that ICE may have additional functions in the regulation of the immune system.

IGIF, an ~ 18-kD polypeptide that stimulates production of interferon-(gamma) (IFN-(gamma)) by T cells (5), is synthesized as a polypeptide precursor (proIGIF) devoid of a conventional signal sequence (6). The precursor of *IGIF* is cleaved after (Asp.sup.35) (6), which suggests that an aspartate-specific protease may be involved. Two families of proteases with substrate specificity for aspartate have been identified; these include the ICE family of cysteine proteases and granzyme B, a serine protease involved in cytotoxic lymphocyte-mediated cell killing and activation of ICE-like cysteine proteases (7, 8). Therefore, we investigated whether one or more of the ICE-family proteases or granzyme B may be involved in the processing of proIGIF and investigated the role that such a cleavage may have in the function of *IGIF*.

We first used transient coexpression in COS cells (9) to determine whether proIGIF could be processed by some of the known ICE-family proteases (Fig. 1A). Coexpression of proIGIF with ICE or its homolog TX (caspase-4) (10) resulted in the cleavage of proIGIF into a polypeptide similar in size to the naturally occurring 18-kD *IGIF*. Single point mutations of the catalytic cysteine residues that inactivate ICE and TX (11) blocked cleavage. Coexpression with CPP32 (caspase-3), a protease involved in programmed cell death (apoptosis) (12), resulted in the cleavage of proIGIF into a ~ 14-kD polypeptide, whereas CMH-1 (caspase-7), a homolog of CPP32 (13), did not appreciably cleave proIGIF. Thus, ICE and TX could cleave proIGIF into a polypeptide similar to the naturally occurring *IGIF*.

We examined the cleavage of proIGIF by these proteases in vitro with the use of purified recombinant ((His).sub.6)-tagged proIGIF as a substrate (14). ICE cleaved the 24-kD proIGIF into two polypeptides of ~ 18 and ~ 6 kD (Fig. 1B). The 18-kD polypeptide comigrated with recombinant mature *IGIF* upon SDS-polyacrylamide gel electrophoresis (PAGE) and contained the same

amino acid residues (Asn-Phe-Gly-Arg-Leu) at its N(H.sub.2)-terminus as did the naturally occurring murine *IGIF*, indicating that ICE cleaved proIGIF at the authentic processing site ((Asp.sup.35-(Asn.sup.36)) (6). This cleavage was specific with a catalytic efficiency ((k.sub.cat)/(K.sub.m), where (K.sub.m) is the Michaelis constant) of 1.4 x (10.sup.7) (M.sup.-1) (s.sup.-1) ((K.sub.m) = 0.6 (+ or -) 0.1 (mu)M; (k.sub.cat) = 8.6 (+ or -) 0.3 (s.sup.-1)) (15) and was inhibited by the specific ICE inhibitors Ac-Tyr-Val-Ala-Asp-aldehyde (2) and Cbz-Val-Ala-Asp-((2,6-dichlorobenzoyl)oxy)methyl ketone (16). Recombinant ((His).sub.6)-tagged human proIGIF was also cleaved by ICE with a similar specificity. Although proIGIF had no detectable IFN-(gamma)-inducing activity, ICE-cleaved proIGIF was active in inducing IFN-(gamma) production in T helper type 1 ((T.sub.H)1) cells (Fig. 1C) (17). TX also cleaved proIGIF into polypeptides of similar size; however, its catalytic efficiency was about two orders of magnitude lower than that of ICE. In a manner consistent with the observation from the COS cell experiments, CPP32 cleaved proIGIF at a different site ((Asp.sup.69)-(Ile.sup.70)) and the resulting polypeptides had little IFN-(gamma)-inducing activity, whereas CMH-1 and granzyme B did not cleave proIGIF. Thus, both in COS cells and in vitro, ICE can process the inactive *IGIF* precursor at the authentic maturation site to generate the biologically active form of *IGIF*.

IGIF is produced by activated Kupffer cells and macrophages in vivo and is exported from the cells upon stimulation by endotoxin (5, 6). We used the COS cell coexpression system to investigate whether the cleavage of proIGIF by ICE would facilitate the export of mature *IGIF*, as in the case of IL-(beta) (2). COS cells coexpressing proIGIF and ICE were labeled with ((sub.35)S)methionine (18). COS cell lysates and conditioned medium were immunoprecipitated with an antiserum to *IGIF* that recognizes both the precursor and the mature form (6) (Fig. 2A). An 18-kD polypeptide corresponding to the mature *IGIF* was detected in the conditioned medium of COS cells coexpressing proIGIF and ICE, whereas COS cells expressing proIGIF alone or with the inactive ICE mutant exported only a very small amount of proIGIF. We estimated by PhosphorImager analysis that ~10% of the mature *IGIF* was exported from transfected cells, whereas < 1% of proIGIF was exported. We also measured the presence of IFN-(gamma)-inducing activity in cell lysates and in the conditioned media of transfected cells (19). IFN-(gamma)-inducing activity was detected in both cell lysates and conditioned medium of COS cells coexpressing proIGIF and ICE, but not those of cells expressing proIGIF or ICE alone (Fig. 2B). The relative amounts of mature *IGIF* in the medium and in cell lysates (19) indicated that the secreted *IGIF* was at least as active as the cytosolic mature *IGIF*. Thus, ICE cleavage of proIGIF can facilitate the export of mature and active *IGIF* from cells.

To study the role of ICE in the activation and export of *IGIF* under physiological conditions, we examined the processing and export of *IGIF* from lipopolysaccharide (LPS)-stimulated Kupffer cells isolated from Propionibacterium acnes-elicited wild-type and (ICE.sup.-/-) mice (20). Although lysates of Kupffer cells from wild-type and (ICE.sup.-/-) mice contained similar amounts of *IGIF* (as determined by an enzyme-linked immunosorbent assay (ELISA) that recognized both proIGIF and mature *IGIF*), *IGIF* was detected in the conditioned medium of wild-type cells but not in that of (ICE.sup.-/-) cells (Fig. 3A). Metabolic labeling and immunoprecipitation experiments confirmed the presence of unprocessed proIGIF in both wild-type and (ICE.sup.-/-) Kupffer cell lysates. However, the 18-kD mature *IGIF* was present only in the conditioned medium of wild-type Kupffer cell cultures and not in that of (ICE.sup.-/-) cultures (Fig. 3B). Similarly, the conditioned medium of LPS-stimulated wild- type adherent splenocytes contained IFN-(gamma)-inducing activity that was sensitive to a neutralizing antibody to *IGIF* (anti-*IGIF*); this activity was reduced in the medium of adherent splenocytes of (ICE.sup.-/-) mice

(Fig. 3C). The absence of *IGIF* in the conditioned medium of (ICE.sup.-/-) Kupffer cells and adherent splenocytes established that the processing of proIGIF by ICE is required for the export of *IGIF*.

The sera of (ICE.sup.-/-) mice stimulated by P. acnes and LPS (21) also contained reduced amounts of *IGIF* (Fig. 4A). This finding may account for the lower concentrations of IFN-(gamma) in the sera of treated (ICE.sup.-/-) mice (Fig. 4B) (22) because we observed no difference between wild-type and (ICE.sup.-/-) mice in the production of IL-12, the other cytokine known to induce IFN-(gamma) (23). Nonadherent splenocytes from wild-type and (ICE.sup.-/-) mice produced similar amounts of IFN-(gamma) when stimulated with *IGIF* in vitro. Administration of recombinant mature *IGIF* (6) into (ICE.sup.-/-) mice restored IFN-(gamma) production in these animals (Fig. 4B) which indicated that the impaired production of IFN-(gamma) was not the result of a defect in the T cells of (ICE.sup.-/-) mice. Moreover, injection of neutralizing anti-*IGIF* suppressed IFN-(gamma) production in wild-type animals stimulated by P. acnes and LPS (Fig. 4C). The defect in IFN-(gamma) production in (ICE.sup.-/-) mice was comparable in magnitude to the defect in IL-1(beta) release, whereas only slight reductions were observed for TNF-(alpha) or IL-6 (3). Thus, ICE is necessary for processing of the *IGIF* precursor and export of active *IGIF*.

IFN-(gamma) and IL-1(beta) are pleiotropic cytokines that contribute to the pathology associated with a variety of infectious, inflammatory, and autoimmune diseases. IFN-(gamma) promotes the activation of macrophages and natural killer cells and contributes to the regulation of T helper cell immune responses, whereas IL-1(beta) stimulates proinflammatory responses in neutrophils, endothelial cells, synovial cells, *osteoclasts*, and other cell types (24). The processing of proIGIF by ICE establishes a link in the regulation of IL-1(beta) and IFN-(gamma) production with implications for monocyte- or macrophage-mediated and T cell-mediated immune functions. IFN-(gamma) can increase the expression of ICE in monocytic cells (25), which suggests a positive-feedback regulation between ICE and IFN-(gamma) that may further enhance the production of *IGIF* and IL-1(beta). However, IFN-(gamma) production by antigen-specific T cells may not be dependent on the ICE-TGIF pathway, because mitogen (concanavalin A) or antigen stimulation of splenic T cells from (ICE.sup.-/-) mice elicited release of normal amounts of IFN-(gamma) (26). T cell proliferation and delayed-type hypersensitivity responses are normal in (ICE.sup.-/-) mice after a secondary exposure to Listeria monocytogenes (22). Thus, the ICE-TGIF pathway of IFN-(gamma) production may be more relevant in vivo to monocyte- or macrophage-mediated inflammatory insults, as opposed to T cell-dependent immune responses.

ICE processing of proIGIF and IFN-(gamma) production may be central events in the pathogenesis of sepsis. Mice lacking IFN-(gamma) or its receptor are resistant to endotoxic shock (27), and neutralizing anti-*IGIF* prevents LPS-induced hepatic injury in P. acres-primed mice (6). These observations suggest that the reduced concentrations of IL-1(beta), *IGIF*, and IFN-(gamma) in LPS-exposed (ICE.sup.-/-) mice (3, 22) account for their increased resistance to LPS-induced sepsis relative to mice lacking a functional IL-1(beta) gene (4), which have a normal septic response. The involvement of ICE in the regulation of these multiple proinflammatory cytokines should be considered in future evaluations of the therapeutic effects of ICE inhibition.

(Figures 1 to 4 ILLUSTRATIONS OMITTED)

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ICE-deficient mice were injected intraperitoneally with 1 mg of heat-killed P. acnes (5). Kupffer cells were prepared 7 days later (31), except that nycodenz gradient was used instead of metrizamide. For each experiment, Kupffer cells (1 x (10.sup.6) cells per milliliter) from two or three animals were pooled and cultured in RPMI 1640 supplemented with 10% FBS and LPS (1 (mu)g/ml; Difco, E. cold strain 055:B5). Cell lysates and conditioned media were prepared 3 hours later. *IGIF* was determined by ELISA with protein G-purified rabbit polyclonal antibody to murine *IGIF* (6). Metabolic labeling and immunoprecipitation experiments were carried out as for COS cells (18) except that methionine-free RPMI 1640 was used in place of DMEM. To prepare conditioned medium of LPS-stimulated adherent splenocytes, we cultured total splenic cells (6 x (10.sup.7) cells in 1 ml) from wild-type or (ICE.sup.-/-) mice for 1 hour. Adherent cells were then stimulated with LPS (50 ng/ml) for 5 hours. Conditioned media were harvested and used at 1:4 dilution in the IFN-(gamma) assay (17) in the presence or absence of anti-*IGIF* (25 (mu)g/ml) (6). (21.) Wild-type or ICE-deficient mice were primed with P. acnes (20). Seven days later, mice were exposed to LPS (1 (mu)g, intravenously). In some experiments, recombinant mature *IGIF* (1 (mu)g) or protein G-purified anti-*IGIF* (250 (mu)g) was coinjected with LPS; sera were collected 3 hours after LPS exposure. (22.) Reduced IFN-(gamma) was also observed in Listeria-infected (N. M. Tsuji et al., in preparation) and LPS-exposed (G. Ku et al., in preparation) (ICE.sup.-/-) mice. (23.) G. Trinchieri, Annul Rev. Immunol. 13, 251 (1995). (24.) F. Belardelli, APMIS 103, 161 (1995); C. A. Dinarello, Blood 87, 2095 (1996). (25.) N. Margolis and C. Dinarello, unpublished data. (26.) G. Ku and M. W. Harding, unpublished data. (27.) D. K. Dalton et al., Science 259, 1739 (1993); S. Huang et al., ibid., p. 1742; B. D. Car et al., J. Exp. Med. 179, 1437 (1994). (28.) Y. Takebe et al., Mol. Cell. Biol. 8, 466 (1988). (29.) Y. Gu, C. Sarnecki, R. A. Aldape, D. J. Livingston, M. S.-S. Su, J. Biol. Chem. 270, 18715 (1995). (30.) H. Quill and R. H. Schwartz, J. Immunol. 138, 3704 (1987). (31.) H. Tsutsui, Y. Mizoguchi, S. Morisawa, Hepato-Gastroenterology 39, 553 (1992).
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2/7/11 (Item 1 from file: 71)
DIALOG(R)File 71:ELSEVIER BIOBASE

00574151 97076975
Interleukin-*18* (*interferon*-*gamma*-*inducing* *factor*) is produced

by osteoblasts and acts via granulocyte/macrophage colony-stimulating factor and not via interferon-gamma to inhibit *osteoclast* formation

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We have established by differential display polymerase chain reaction of mRNA that interleukin (*IL*)-*18* is expressed by osteoblastic stroma cells. The stromal cell populations used for comparison differed in their ability to promote *osteoclast*-like multinucleated cell (OCL) formation. mRNA for *IL*-*18* was found to be expressed in greater abundance in lines that were unable to support OCL formation than in supportive cells. Recombinant *IL*-*18* was found to inhibit OCL formation in cocultures of osteoblasts and hemopoietic cells of spleen or bone marrow origin. *IL*-*18* inhibited OCL formation in the presence of *osteoclastogenic* agents including, 1alpha, 25-dihydroxyvitamin Dinf 3, prostaglandin Einf 2, parathyroid hormone, IL-1, and IL-11. The inhibitory effect of *IL*-*18* was limited to the early phase of the cocultures, which coincides with proliferation of hemopoietic precursors. *IL*-*18* has been reported to induce interferon-gamma (IFN-gamma) and granulocyte/macrophage colony-stimulating factor (GM-CSF) production in T cells, and both agents also inhibit OCL formation in vitro. Neutralizing antibodies to GM-CSF were able to rescue *IL*-*18* inhibition of OCL formation, whereas neutralizing antibodies to IFN-gamma did not. It cocultures with osteoblasts and spleen cells from IFN- gamma receptor type II-deficient mice, *IL*-*18* was found to inhibit OCL formation, indicating that *IL*-*18* acted independently of IFN-gamma production; IFN-gamma had no effect in these cocultures. Additionally, in cocultures in which spleen cells were derived from receptor-deficient mice and osteoblasts were from wild- type mice and vice versa, we identified that the target cells for IFN-gamma inhibition of OCL formation were the hemepoietic cells. The work provides evidence that *IL*-*18* is expressed by osteoblasts and inhibits OCL formation via GM-CSF production and not via IFN-gamma production.

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DIALOG(R)File 73:EMBASE

07173645 EMBASE No: 1998059693
Interleukin *18* inhibits *osteoclast* formation via T cell production of granulocyte macrophage colony-stimulating factor

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IL-*18* inhibits *osteoclast* (OCL) formation in vitro independent of IFN- gamma production, and this was abolished by the addition of neutralizing antibodies to GM-CSF. We now establish that *IL*-*18* was unable to inhibit OCL formation in cocultures using GM-CSF-deficient mice (GM-CSF-/-). Reciprocal cocultures using either wild-type osteoblasts with GM-CSF -/- spleen cells or GM-CSF -/- osteoblasts with wild-type spleen cells were examined. Wild-type spleen cells were required to elicit a response to *IL*-*18* indicating that cells of splenic origin were the *IL* -*18* target. As T cells comprise a large proportion of the spleen cell population, the role of T cells in *osteoclastogenesis* was examined. Total T cells were removed and repleted in various combinations. Addition of wild-type T cells to a GM-CSF -/- coculture restored *IL*-*18* inhibition of *osteoclastogenesis*. Major subsets of T cells, CD4sup + and CD8sup +, were also individually depleted. Addition of either CD4sup + or CD8sup + wild-type T cells restored *IL*-*18* action in a GM-CSF -/- background, while *IL*-*18* was ineffective when either CD4sup + or CD8sup + GM-CSF -/- T cells were added to a wild-type coculture. These results highlight the involvement of T cells in *IL*-*18*-induced OCL inhibition and provide evidence for a new OCL inhibitory pathway whereby *IL*-*18* inhibits OCL formation due to action upon T cells promoting the release of GM-CSF, which in turn acts upon OCL precursors.

2/7/13 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

07120926 EMBASE No: 1998008404
Cytokines in the pathogenesis of osteoporosis
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06812899 EMBASE No: 1997095390
Interleukin-*18* (*interferon*-*gamma*-*inducing* *factor*) is produced by osteoblasts and acts via granulocyte/macrophage colony-stimulating factor and not via interferon-gamma to inhibit *osteoclast* formation
Udagawa N.; Horwood N.J.; Elliott J.; Mackay A.; Owens J.; Okamura H.; Kurimoto M.; Chambers T.J.; Martin T.J.; Gillespie M.T.
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We have established by differential display polymerase chain reaction of mRNA that interleukin (*IL*)-*18* is expressed by osteoblastic stroma cells. The stromal cell populations used for comparison differed in their ability to promote *osteoclast*-like multinucleated cell (OCL) formation. mRNA for *IL*-*18* was found to be expressed in greater abundance in lines that were unable to support OCL formation than in supportive cells. Recombinant *IL*-*18* was found to inhibit OCL formation in cocultures of osteoblasts and hemopoietic cells of spleen or bone marrow origin. *IL*-*18* inhibited OCL formation in the presence of *osteoclastogenic* agents including, 1alpha, 25-dihydroxyvitamin Dinf 3, prostaglandin Einf 2, parathyroid hormone, IL-1, and IL-11. The inhibitory effect of *IL*-*18* was limited to the early phase of the cocultures, which coincides with proliferation of hemopoietic precursors. *IL*-*18* has been reported to induce interferon-gamma (IFN-gamma) and granulocyte/macrophage colony-stimulating factor (GM-CSF) production in T cells, and both agents also inhibit OCL formation in vitro. Neutralizing antibodies to GM-CSF were able to rescue *IL*-*18* inhibition of OCL formation, whereas neutralizing antibodies to IFN-gamma did not. It cocultures with osteoblasts and spleen cells from IFN- gamma receptor type II-deficient mice, *IL*-*18* was found to inhibit OCL formation, indicating that *IL*-*18* acted independently of IFN-gamma production; IFN-gamma had no effect in these cocultures. Additionally, in cocultures in which spleen cells were derived from receptor-deficient mice and osteoblasts were from wild- type mice and vice versa, we identified that the target cells for IFN-gamma inhibition of OCL formation were the hemepoietic cells. The work provides evidence that *IL*-*18* is expressed by osteoblasts and inhibits OCL formation via GM-CSF production and not via IFN-gamma production.

2/7/15 (Item 1 from file: 76)
DIALOG(R)File 76:Life Sciences Collection

02301532 4376053
Interleukins in the control of *osteoclast* differentiation
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To maintain homeostasis of bone, the production of osteoblasts and *osteoclasts* is tightly regulated. At the local level, hormones and cytokines control formation of *osteoclasts* from hemopoietic precursors by acting upon osteoblastic-stromal cells and in some cases also upon cells of the immune system. Osteoblasts regulate *osteoclast* formation by providing physical support and cytokines such as M-CSF and IL-11, which promote *osteoclast* differentiation. Osteoblasts are also a source of *IL*-*18*, which limits *osteoclast* formation. The requirement of contact between osteoblasts and hemopoietic cells for successful *osteoclast* formation led to a concept of a membrane-anchored stromal cell molecule that programs *osteoclast* differentiation. This mechanism has been highlighted by the discovery of osteoprotegerin (OPG), a soluble tumor necrosis factor (TNF)

family member that inhibits *osteoclast* formation. The ligand for OPG is a novel transmembrane TNF receptor superfamily member, the *osteoclast* differentiating factor (ODF). The recognition of the osteoprotegerin/osteoprotegerin-ligand axis will lead to new insights into the control of *osteoclast* differentiation by interleukins.

2/7/16 (Item 2 from file: 76)
DIALOG(R)File 76:Life Sciences Collection

02281756 4329956
Interleukin *18* inhibits *osteoclast* formation via T cell production of granulocyte macrophage colony-stimulating factor
Horwood, N.J.; Udagawa, N.; Elliott, J.; Grail, D.; Okamura, H.; Kurimoto, M.; Dunn, A.R.; Martin, T.J.; Gillespie, M.T.
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SUBFILE: Immunology Abstracts

IL-*18* inhibits *osteoclast* (OCL) formation in vitro independent of IFN- gamma production, and this was abolished by the addition of neutralizing antibodies to GM-CSF. We now establish that *IL*-*18* was unable to inhibit OCL formation in cocultures using GM-CSF-deficient mice (GM-CSF -/-). Reciprocal cocultures using either wild-type osteoblasts with GM-CSF -/- spleen cells or GM-CSF -/- osteoblasts with wild-type spleen cells were examined. Wild-type spleen cells were required to elicit a response to *IL*-*18* indicating that cells of splenic origin were the *IL* -*18* target. As T cells comprise a large proportion of the spleen cell population, the role of T cells in *osteoclastogenesis* was examined. Total T cells were removed and repleted in various combinations. Addition of wild-type T cells to a GM-CSF -/- coculture restored *IL*-*18* inhibition of *osteoclastogenesis*. Major subsets of T cells, CD4 super(+) and CD8 super(+), were also individually depleted. Addition of either CD4 super(+) or CD8 super(+) wild-type T cells restored *IL*-*18* action in a GM-CSF -/- background, while *IL*-*18* was ineffective when either CD4 super(+) or CD8 super(+) GM-CSF -/- T cells were added to a wild-type coculture. These results highlight the involvement of T cells in *IL*-*18*-induced OCL inhibition and provide evidence for a new OCL inhibitory pathway whereby *IL*-*18* inhibits OCL formation due to action upon T cells promoting the release of GM-CSF, which in turn acts upon OCL precursors.

2/7/17 (Item 3 from file: 76)
DIALOG(R)File 76:Life Sciences Collection

02159460 4077457
Interleukin-*18* (*interferon*- *gamma* -*inducing* *factor*) is produced by osteoblasts and acts via granulocyte/macrophage colony-stimulating factor and not via interferon- gamma to inhibit *osteoclast* formation
Udagawa, N.; Horwood, N.J.; Elliot, J.; Mackay, A.; Owens, J.; Okamura, H.; Kurimoto, M.; Chambers, T.J.; Martin, T.J.; Gillespie, M.T.
St. Vincent's Inst. Med. Res., 14 Victoria Parade, Fitzroy 3065, Vic., Australia
J. EXP. MED. vol. 185, no. 6, pp. 1005-1112 (1997)
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DOCUMENT TYPE: Journal article LANGUAGE: ENGLISH
SUBFILE: Immunology Abstracts

We have established by differential display polymerase chain reaction of mRNA that interleukin (*IL*)-*18* is expressed by osteoblastic stromal cells. The stromal cell populations used for comparison differed in their ability to promote *osteoclast*-like multinucleated cell (OCL) formation. mRNA for *IL*-*18* was found to be expressed in greater abundance in lines that were unable to support OCL formation than in supportive cells. Recombinant *IL*-*18* was found to inhibit OCL formation in cocultures of osteoblasts and hemopoietic cells of spleen or bone marrow origin. *IL*-*18* inhibited OCL formation in the presence of *osteoclastogenic* agents including 1 alpha ,25-dihydroxyvitamin D sub(3), prostaglandin E sub(2), parathyroid hormone, IL-1, and IL-11. The inhibitory effect of *IL*-*18* was limited to the early phase of the cocultures, which coincides with proliferation of hemopoietic precursors. *IL*-*18* has been reported to induce interferon- gamma (IFN- gamma) and granulocyte/macrophage colony-stimulating factor (GM-CSF) production in T cells, and both agents also inhibit OCL formation in vitro. Neutralizing antibodies to GM-CSF were able to rescue *IL*-*18* inhibition of OCL formation, whereas neutralizing antibodies to IFN- gamma did not. In cocultures with osteoblasts and spleen cells from IFN- gamma receptor type II-deficient mice, *IL*-*18* was found to inhibit OCL formation, indicating that *IL*-*18* acted independently of IFN- gamma production: IFN- gamma had no effect in these cocultures. Additionally, in cocultures in which spleen cells were derived from receptor-deficient mice and osteoblasts were from wild-type mice and vice versa, we identified that the target cells for IFN- gamma inhibition of OCL formation were the hemopoietic cells. The work provides evidence that *IL*-*18* is expressed by osteoblasts and inhibits OCL formation via GM-CSF production and not via IFN- gamma production.

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DIALOG(R)File 94:JICST-EPlus

04464911 JICST ACCESSION NUMBER: 98A0028829 FILE SEGMENT: JICST-E
IL-*18* (IFN-.GAMMA. inducer) directly affects *osteoclast* progenitor cells and suppresses differentiation of *osteoclasts* through GM-CSF production.
UDAGAWA NOBUYUKI (1); HORWOOD N J (1); MARTIN T J (1); GILLESPIE M T (1); SUDA TATSUO (2); KURIMOTO MASASHI (3); OKAMURA HARUKI (4); CHAMBERS T J (5)
(1) St.Vincent'sIgakuken; (2) Showa Univ., Sch. of Dent.; (3) Hayashibara Biochem. Lab., Inc.; (4)Hyogo Coll. of Med.; (5) St.George'sIgakuken
Osteoporosis Jpn, 1997, VOL.5,NO.4, PAGE.760-762, FIG.2, REF.7
JOURNAL NUMBER: L3145AAU ISSN NO: 0919-6307
UNIVERSAL DECIMAL CLASSIFICATION: 577.175.1
LANGUAGE: Japanese COUNTRY OF PUBLICATION: Japan
DOCUMENT TYPE: Journal
ARTICLE TYPE: Short Communication
MEDIA TYPE: Printed Publication

2/7/19 (Item 2 from file: 94)
DIALOG(R)File 94:JICST-EPlus

03930639 JICST ACCESSION NUMBER: 97A0715971 FILE SEGMENT: PreJICST-E
IL-*18* (IFN-.GAMMA. inducer) directly affects in *osteoclastic*

precursor cells and suppresses *osteoclastic* differentiation through GM-CSF production.
UDAGAWA NOBUYUKI (1); HORWOOD N J (1); MARTIN T J (1); GILLESPIE M T (1); SUDA TATSUO (2); KURIMOTO MASASHI (3); OKAMURA HARUKI (4); CHAMBERS T J (5)
(1) St.Vincent'sIgakuken; (2) Showa Univ., Sch. of Dent.; (3) Hayashibara Biochem. Lab., Inc.; (4)Hyogo Coll. of Med.; (5) St.George'sIgakuken
Nippon Kotsu Taisha Gakkai Zasshi(Journal of Bone and Mineral Metabolism), 1997, VOL.15,NO.2, PAGE.79
JOURNAL NUMBER: X0157AAW   ISSN NO: 0910-0067
LANGUAGE: Japanese   COUNTRY OF PUBLICATION: Japan
DOCUMENT TYPE: Journal
MEDIA TYPE: Printed Publication

2/7/20 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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09747848 98425700
Interleukin-*18*: perspectives on the newest interleukin.
Gillespie MT; Horwood NJ
St. Vincent's Institute of Medical Research and The University of Melbourne, Department of Medicine, St. Vincent's Hospital, Fitzroy, Vic, Australia. m.gillespie@medicine.unimelb.edu.au
Cytokine Growth Factor Rev (ENGLAND) Jun 1998, 9 (2) p109-16, ISSN 1359-6101 Journal Code: CF7
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
Just over two years ago the newest member of the interleukin family of cytokines, *IL*-*18*, was molecularly cloned. *IL*-*18* was originally identified as a result of its ability to induce interferon gamma production, however with the advent of its cloning and the production of recombinant protein a number of other biological actions have since been identified. Recently the receptor for *IL*-*18* was also characterised. Due to the structural and biological properties shared between *IL*-*18* and IL-1 and their respective receptors, questions relating to *IL*-*18* activities are being answered at a rapid pace. This article addresses the biology of *IL*-*18* in both disease and non-disease states. (48 Refs.)

2/7/21 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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09705258 98380602
Interleukins in the control of *osteoclast* differentiation.
Martin TJ; Romas E; Gillespie MT
St. Vincent's Institute of Medical Research, Victoria, Australia.
Crit Rev Eukaryot Gene Expr (UNITED STATES) 1998, 8 (2) p107-23, ISSN 1045-4403 Journal Code: BEJ
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, ACADEMIC
To maintain homeostasis of bone, the production of osteoblasts and *osteoclasts* is tightly regulated. At the local level, hormones and cytokines control formation of *osteoclasts* from hemopoietic precursors by acting upon osteoblastic-stromal cells and in some cases also upon cells of the immune system. Osteoblasts regulate *osteoclast* formation by providing physical support and cytokines such as M-CSF and IL-11, which promote *osteoclast* differentiation. Osteoblasts are also a source of *IL*-*18*,

which limits *osteoclast* formation. The requirement of contact between osteoblasts and hemopoietic cells for successful *osteoclast* formation led to a concept of a membrane-anchored stromal cell molecule that programs *osteoclast* differentiation. This mechanism has been highlighted by the discovery of osteoprotegerin (OPG), a soluble tumor necrosis factor (TNF) family member that inhibits *osteoclast* formation. The ligand for OPG is a novel transmembrane TNF receptor superfamily member, the *osteoclast* differentiating factor (ODF). The recognition of the osteoprotegerin/osteoprotegerin-ligand axis will lead to new insights into the control of *osteoclast* differentiation by interleukins. (143 Refs.)

2/7/22 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09694363 98119851
Interleukin *18* inhibits *osteoclast* formation via T cell production of granulocyte macrophage colony-stimulating factor.
Horwood NJ; Udagawa N; Elliott J; Grail D; Okamura H; Kurimoto M; Dunn AR ; Martin T; Gillespie MT
St. Vincent's Institute of Medical Research and The University of Melbourne, Department of Medicine, St. Vincent's Hospital, Fitzroy, Victoria 3065, Australia.
J Clin Invest (UNITED STATES) Feb 1 1998, 101 (3) p595-603, ISSN 0021-9738 Journal Code: HS7
Languages: ENGLISH
Document type: JOURNAL ARTICLE
IL-*18* inhibits *osteoclast* (OCL) formation in vitro independent of IFN-gamma production, and this was abolished by the addition of neutralizing antibodies to GM-CSF. We now establish that *IL*-*18* was unable to inhibit OCL formation in cocultures using GM-CSF-deficient mice (GM-CSF -/-). Reciprocal cocultures using either wild-type osteoblasts with GM-CSF -/- spleen cells or GM-CSF -/- osteoblasts with wild-type spleen cells were examined. Wild-type spleen cells were required to elicit a response to *IL*-*18* indicating that cells of splenic origin were the *IL* -*18* target. As T cells comprise a large proportion of the spleen cell population, the role of T cells in *osteoclastogenesis* was examined. Total T cells were removed and repleted in various combinations. Addition of wild-type T cells to a GM-CSF -/- coculture restored *IL*-*18* inhibition of *osteoclastogenesis*. Major subsets of T cells, CD4+ and CD8+, were also individually depleted. Addition of either CD4+ or CD8+ wild-type T cells restored *IL*-*18* action in a GM-CSF -/- background, while *IL*-*18* was ineffective when either CD4+ or CD8+ GM-CSF -/- T cells were added to a wild-type coculture. These results highlight the involvement of T cells in *IL*-*18* -induced OCL inhibition and provide evidence for a new OCL inhibitory pathway whereby *IL*-*18* inhibits OCL formation due to action upon T cells promoting the release of GM-CSF, which in turn acts upon OCL precursors.

2/7/23 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09684560 97228136
Interleukin-*18* (*interferon*-*gamma*-*inducing* *factor*) is produced by osteoblasts and acts via granulocyte/macrophage colony-stimulating factor and not via interferon-gamma to inhibit *osteoclast* formation.
Udagawa N; Horwood NJ; Elliott J; Mackay A; Owens J; Okamura H; Kurimoto

M; Chambers TJ; Martin TJ; Gillespie MT
St. Vincent's Institute of Medical Research and The University of Melbourne, Department of Medicine, Victoria, Australia.
J Exp Med (UNITED STATES) Mar 17 1997, 185 (6) p1005-12, ISSN 0022-1007 Journal Code: I2V
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We have established by differential display polymerase chain reaction of mRNA that interleukin (*IL*)-*18* is expressed by osteoblastic stromal cells. The stromal cell populations used for comparison differed in their ability to promote *osteoclast*-like multinucleated cell (OCL) formation. mRNA for *IL*-*18* was found to be expressed in greater abundance in lines that were unable to support OCL formation than in supportive cells. Recombinant *IL*-*18* was found to inhibit OCL formation in cocultures of osteoblasts and hemopoietic cells of spleen or bone marrow origin. *IL*-*18* inhibited OCL formation in the presence of *osteoclastogenic* agents including 1alpha,25-dihydroxyvitamin D3, prostaglandin E2, parathyroid hormone, IL-1, and IL-11. The inhibitory effect of *IL*-*18* was limited to the early phase of the cocultures, which coincides with proliferation of hemopoietic precursors. *IL*-*18* has been reported to induce interferon-gamma (IFN-gamma) and granulocyte/macrophage colony-stimulating factor (GM-CSF) production in T cells, and both agents also inhibit OCL formation in vitro. Neutralizing antibodies to GM-CSF were able to rescue *IL*-*18* inhibition of OCL formation, whereas neutralizing antibodies to IFN-gamma did not. In cocultures with osteoblasts and spleen cells from IFN-gamma receptor type II-deficient mice, *IL*-*18* was found to inhibit OCL formation, indicating that *IL*-*18* acted independently of IFN-gamma production: IFN-gamma had no effect in these cocultures. Additionally, in cocultures in which spleen cells were derived from receptor-deficient mice and osteoblasts were from wild-type mice and vice versa, we identified that the target cells for IFN-gamma inhibition of OCL formation were the hemopoietic cells. The work provides evidence that *IL*-*18* is expressed by osteoblasts and inhibits OCL formation via GM-CSF production and not via IFN-gamma production.

2/7/24 (Item 1 from file: 351)
DIALOG(R)File 351:DERWENT WPI

012032054
WPI Acc No: 98-448964/199839
Use of *interleukin*-*18* to inhibit *osteoclast* formation - in treatment of e.g. hypercalcaemia, *osteoclastoma*, Behcet's syndrome, osteosarcoma, chronic rheumatoid arthritis, deformity ostitis, primary hyperthyroidism and osteoporosis
Patent Assignee: HAYASHIBARA SEIBUTSU KAGAKU (HAYB)
Inventor: GILLESPIE M T; HORWOOD N J; KURIMOTO M; UDAGAWA N
Number of Countries: 025 Number of Patents: 002
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Main IPC	Week
EP 861663	A2	19980902	EP 98301352	A	19980224	A61K-038/20	199839 B
JP 10236974	A	19980908	JP 9755468	A	19970225	A61K-038/00	199846

Priority Applications (No Type Date): JP 9755468 A 19970225
Patent Details:

Patent	Kind	Lan	Pg	Filing Notes	Application	Patent
EP 861663	A2	E	56			

Designated States (Regional): AL AT BE CH DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI

JP 10236974 A 24

Abstract (Basic): EP 861663 A

Use of *interleukin*-*18* (*IL*-*18*) or a functional equivalent for inhibition of *osteoclast* formation is new.

USE - *IL*-*18* is used for treating or preventing *osteoclast* -related diseases (claimed) e.g. hypercalcaemia, *osteoclastoma* Behcet's syndrome, osteosarcoma, arthropathy, chronic rheumatoid arthritis, deformity ostitis, primary hyperthyroidism, osteopaenia and osteoporosis. *IL*-*18* is administered orally, intradermally, subcutaneously, muscularly or intravenously at a dosage of 0.5 mu g to 100 mg (preferably 2 mu g to 10 mg) 2-6 times a day.

Dwg.0/5

Derwent Class: B04; D16

International Patent Class (Main): A61K-038/00; A61K-038/20

International Patent Class (Additional): C07K-014/54; C12N-015/09

2/7/25 (Item 1 from file: 370)

DIALOG(R)File 370:Science

00501040 (USE 9 FOR FULLTEXT)

Activation of *Interferon*- (*gamma*) *Inducing* *Factor* Mediated by Interleukin-1 (beta) Converting Enzyme

Gu, Yong; Kuida, Keisuke; Tsutsui, Hiroko; Ku, George; Hsiao, Kathy; Fleming, Mark A.; Hayashi, Nobuki; Higashino, Kazuya; Okamura, Haruki; Nakanishi, Kenji; Kurimoto, Masashi; Tanimoto, Tadao; Flavell, Richard A. ; Sato, Vicki; Harding, Matthew W.; Livingston, David J.; Su, Michael S.-S.

Y. Gu, G. Ku, K. Hsiao, M. A. Fleming, V. Sato, M. W. Harding, D. J. Livingston, M. S.-S. Su, Vertex Pharmaceuticals Inc., 130 Waverly Street, Cambridge, MA 02139, USA. ; K. Kuida, Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan. ; H. Tsutsui, N. Hayashi, K. Higashino, H. Okamura, K. Nakanishi, Hyogo College of Medicine, 1-1, Mukogawa-cho, Nishinomiya, Japan. ; M. Kurimoto and T. Tanimoto, Fujisaki Institute, Hayashibara Biochemical Laboratories, Hayashibara Company Inc., Okayama, Japan. ; R. A. Flavell, Howard Hughes Medical Institute, Yale University School of Medicine, New Haven, CT 06510, USA.

Science Vol. 275 5297 pp. 206

Publication Date: 1-10-1997 (970110) Publication Year: 1997

Document Type: Journal ISSN: 0036-8075

Language: English

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Word Count: 2474

Abstract: The interleukin-1 (beta) (IL-1 (beta)) converting enzyme (ICE) processes the inactive IL-1 (beta) precursor to the proinflammatory cytokine. ICE was also shown to cleave the precursor of *interferon*- (*gamma*) *inducing* *factor* (*IGIF*) at the authentic processing site with high efficiency, thereby activating *IGIF* and facilitating its export. Lipopolysaccharide-activated ICE-deficient (ICE.sup(-/-)) Kupffer cells synthesized the *IGIF* precursor but failed to process it into the active form. Interferon- (gamma) and *IGIF* were diminished in the sera of ICE.sup(-/-) mice exposed to Propionibacterium acnes and lipopolysaccharide. The lack of multiple proinflammatory cytokines in ICE.sup(-/-) mice may account for their protection from septic shock

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9. A 0.6-kb cDNA encoding full-length murine proIGIF (B6) was ligated into the mammalian expression vector pCDLSRa (B28) . Plasmids for the expression of active human ICE (B11) , TX (B10) , and CMH-1 (B13) lacking the prosequence were as described. Expression plasmid for the active form of CPP32 lacking the prosequence (B12) was constructed similarly in the pCDLSRa vector. Plasmids (3 (mu) g) were transfected into COS cells in 35-mm dishes by the DEAE-dextran method (B11) . Twenty-four hours later, cells were lysed and the lysates were subjected to SDS-PAGE and immunoblotting with an antiserum to *IGIF* (B6) . ;
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14. Expression plasmid for (His).inf(6)-proIGIF was created by introducing Nde I sites at the ends of murine proIGIF cDNA coding sequence (B6) and ligating into Escherichia coli expression vector pET-15B (Novagen). The E. coli strain BL21(DE3) carrying the plasmid was induced with isopropyl-1-thio- (beta) -d-galactopyranoside. (His).inf(6)-proIGIF protein was purified from soluble fractions by Ni-nitrilotriacetic acid-agarose (Qiagen) chromatography according to the manufacturer's instructions. In vitro cleavage reactions by ICE and ICE-like proteases were carried out as in (B29) . Conditions for cleavage by granzyme B were as in (B8) . Cleavage products were analyzed by SDS-PAGE on 16% gels and Coomassie blue staining and were subjected to NH.inf(2)-terminal amino acid sequencing with an ABI automated peptide sequencer. ;
15. [.sup(35)S]methionine-labeled proIGIF [~3000 cpm, prepared by in vitro transcription and translation with the TNT T7 coupled reticulocyte lysate system (Promega) and proIGIF cDNA in pSP73 vector as template] was incubated in reaction mixtures of 60 (mu) l containing 0.1 to 1 nM recombinant ICE and 190 nM to 12 (mu) M unlabeled proIGIF for 8 to 10 min at 37.Deg.C. Cleavage product concentrations were determined by SDS-PAGE and PhosphorImager analysis. The kinetic parameters were calculated by nonlinear regression fitting of the rate versus concentration data to the Michaelis-Menten equation by means of the program Enzfitter (Biosoft). ;
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17. The T.inf(H)1 A. E7 cells (B30) (1.3 x 10.sup(5) cells in 0.15 ml) or nonadherent splenic T cells (8 x 10.sup(5) cells) in 96-well plates were treated with *IGIF* or conditioned medium for 18 to 20 hours, and the culture supernatants were assayed for IFN- (gamma) by ELISA (Endogen, Cambridge, MA). ;
18. COS cells (3.5 x 10.sup(5) cells in a 35-mm dish) were labeled for 7 hours with 1 ml of methionine-free Dulbecco's modified Eagle's medium (DMEM) containing 2.5% normal DMEM, 1% dialyzed fetal bovine serum (FBS), and [.sup(35)S]methionine (300 (mu) Ci/ml; [.sup(35)S]Express Protein

Labeling Mix, New England Nuclear). Cell lysates [prepared in 20 mM Hepes (pH 7.2), 150 mM NaCl, 0.1% Triton X-100, 5 mM N-ethylmaleimide, 1 mM phenylmethylsulfonyl fluoride, and leupeptin (2.5 (mu) g/ml)] or conditioned medium were immunoprecipitated with the antiserum to *IGIF* (B6) . ;
19. COS cells (3.5 x 10.sup(5) cells in a 35-mm dish) were transfected and grown in 1 ml of medium for 18 hours. Medium was harvested and used at 1:10 final dilution in the IFN- (gamma) induction assay (B17) ; COS cell pellets from the same transfection were lysed in 100 (mu) l of 20 mM Hepes (pH 7.0) by three cycles of freezing and thawing. Lysates were cleared by centrifugation and were used at 1:10 dilution in the assay. On the basis of our analysis that 10% mature *IGIF* was exported out of the cells, we estimated that the mature *IGIF* concentration in lysates is ~90 times that of the conditioned medium. ;
20. Wild-type or ICE-deficient mice were injected intraperitoneally with 1 mg of heat-killed P. acnes (B5) . Kupffer cells were prepared 7 days later (B31) , except that nycodenz gradient was used instead of metrizamide. For each experiment, Kupffer cells (1 x 10.sup(6) cells per milliliter) from two or three animals were pooled and cultured in RPMI 1640 supplemented with 10% FBS and LPS (1 (mu) g/ml; Difco, E. coli strain 055:B5). Cell lysates and conditioned media were prepared 3 hours later. *IGIF* was determined by ELISA with protein G-purified rabbit polyclonal antibody to murine *IGIF* (B6) . Metabolic labeling and immunoprecipitation experiments were carried out as for COS cells (B18) except that methionine-free RPMI 1640 was used in place of DMEM. To prepare conditioned medium of LPS-stimulated adherent splenocytes, we cultured total splenic cells (6 x 10.sup(7) cells in 1 ml) from wild-type or ICE.sup(-/-) mice for 1 hour. Adherent cells were then stimulated with LPS (50 ng/ml) for 5 hours. Conditioned media were harvested and used at 1:4 dilution in the IFN- (gamma) assay (B17) in the presence or absence of anti-*IGIF* (25 (mu) g/ml) (B6) . ;
21. Wild-type or ICE-deficient mice were primed with P. acnes (B20) . Seven days later, mice were exposed to LPS (1 (mu) g, intravenously). In some experiments, recombinant mature *IGIF* (1 (mu) g) or protein G-purified anti-*IGIF* (250 (mu) g) was coinjected with LPS; sera were collected 3 hours after LPS exposure. ;
22. Reduced IFN- (gamma) was also observed in Listeria-infected (N. M. Tsuji et al., in preparation) and LPS-exposed (G. Ku et al., in preparation) ICE.sup(-/-) mice. ;
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32. We thank T. Fox and W. Chen for ICE and TX protein; A. Diu, C. Faucheu, and J.-L. Lalanne for TX cDNA; M. Rincon for A. E7 cells; J. Lippke for CPP32 and CMH-1 cDNA; B. O'Hare for oligonucleotide synthesis and DNA sequencing; T. Faust for ELISA; A. Heiser for animal surgery; and J. Boger for critical reading and discussion of the manuscript. R.A.F. is an HHMI Investigator.

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09195096
ISSN: 0021-9738
JOURNAL: JOURNAL OF CLINICAL INVESTIGATION
(TABLE OF CONTENTS RECORD)
(The Complete Table of Contents now Available in Format 19)

2/7/27 (Item 2 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

09195081 GENUINE ARTICLE#: YW195 NUMBER OF REFERENCES: 25
TITLE: *Interleukin* *18* inhibits *osteoclast* formation via T cell production of granulocyte macrophage colony-stimulating factor
AUTHOR(S): Horwood NJ; Udagawa N; Elliott J; Grail D; Okamura H; Kurimoto M ; Dunn AR; Martin TJ; Gillespie MT (REPRINT)
CORPORATE SOURCE: ST VINCENTS INST MED RES,41 VICTORIA PARADE/FITZROY/VIC 3065/AUSTRALIA/ (REPRINT); ST VINCENTS INST MED RES,/FITZROY/VIC 3065/AUSTRALIA/; UNIV MELBOURNE,ST VINCENTS HOSP, DEPT MED/FITZROY/VIC 3065/AUSTRALIA/; SHOWA UNIV,SCH DENT, DEPT BIOCHEM/TOKYO 142//JAPAN/; LUDWIG INST CANC RES,/PARKVILLE/VIC 3052/AUSTRALIA/; HYOGO MED UNIV,DEPT IMMUNOL & MED ZOOL/NISHINOMIYA/HYOGO 663/JAPAN/; HAYASHIBARA BIOCHEM LABS INC,FUJISAKI INST/OKAYAMA 702//JAPAN/
PUBLICATION TYPE: JOURNAL
PUBLICATION: JOURNAL OF CLINICAL INVESTIGATION, 1998, V101, N3 (FEB 1), P 595-603
PUBLISHER: ROCKEFELLER UNIV PRESS, 1114 FIRST AVE, 4TH FL, NEW YORK, NY 10021
ISSN: 0021-9738
CURRENT CONTENTS JOURNAL ANNOUNCEMENT: CC LIFE, V41, N10
LANGUAGE: English DOCUMENT TYPE: ARTICLE
ABSTRACT: *IL*-*18* inhibits *osteoclast* (OCL) formation in vitro independent of IFN-gamma production, and this was abolished by the addition of neutralizing antibodies to GM-CSF, We now establish that *IL*-*18* was unable to inhibit OCL formation in cocultures using GM-CSF-deficient mice (GM-CSF -/-). Reciprocal cocultures using either wild-type osteoblasts with GM-CSF -/- spleen cells or GM-CSF -/- osteoblasts with wild-type spleen cells were examined. Wild-type spleen cells were required to elicit a response to *IL*-*18* indicating that cells of splenic origin were the *IL*-*18* target. As T cells comprise a large proportion of the spleen cell population, the role of T cells in *osteoclastogenesis* was examined. Total T cells were removed and repleted in various combinations, Addition of wild-type T cells to a GM-CSF -/- coculture restored *IL*-*18* inhibition of *osteoclastogenesis*, Major subsets of T cells, CD4(+) and CD8(+), were also individually depleted, Addition of either CD4(+) or CD8(+) wildtype T cells restored *IL*-*18* action in a GM-CSF -/- background, while *IL*-*18* was ineffective when either CD4(+) or CD8(+) GM-CSF -/- T cells were added to a wild-type coculture. These results highlight the involvement of T cells in *IL*-*18*-induced OCL inhibition and provide evidence for a new OCL inhibitory pathway whereby *IL*-*18* inhibits OCL formation due to action upon T cells promoting the release of GM-CSF, which in turn acts upon OCL precursors.

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DIALOG(R)File 440:Current Contents Search(R)

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DIALOG(R)File 440:Current Contents Search(R)

08296587 GENUINE ARTICLE#: WP404 NUMBER OF REFERENCES: 39
TITLE: *Interleukin*-*18* (*interferon*-*gamma*-*inducing* *factor*) is produced by osteoblasts and acts via granulocyte/macrophage colony-stimulating factor and not via interferon-gamma to inhibit *osteoclast* formation
AUTHOR(S): Udagawa N; Horwood NJ; Elliott J; Mackay A; Owens J; Okamura H; Kurimoto M; Chambers TJ; Martin TJ; Gillespie MT (REPRINT)
CORPORATE SOURCE: ST VINCENTS INST MED RES,41 VICTORIA PARADE/FITZROY/VIC 3065/AUSTRALIA/ (REPRINT); ST VINCENTS INST MED RES,/FITZROY/VIC 3065/AUSTRALIA/; UNIV MELBOURNE,ST VINCENTS HOSP, DEPT MED/FITZROY/VIC 3065/AUSTRALIA/; ST GEORGE HOSP,SCH MED, DEPT HISTOPATHOL/LONDON SW17 0RE//ENGLAND/; HYOGO MED UNIV,DEPT BACTERIOL/NISHINOMIYA/HYOGO 663/JAPAN/; HAYASHIBARA BIOCHEM LABS INC,FUJISAKI INST/OKAYAMA 702//JAPAN/
PUBLICATION TYPE: JOURNAL
PUBLICATION: JOURNAL OF EXPERIMENTAL MEDICINE, 1997, V185, N6 (MAR 17), P 1005-1012
PUBLISHER: ROCKEFELLER UNIV PRESS, 1114 FIRST AVE, 4TH FL, NEW YORK, NY 10021
ISSN: 0022-1007
CURRENT CONTENTS JOURNAL ANNOUNCEMENT: CC LIFE, V40, N16
LANGUAGE: English DOCUMENT TYPE: ARTICLE
ABSTRACT: We have established by differential display polymerase chain reaction of mRNA that interleukin (*IL*)-*18* is expressed by osteoblastic stromal cells. The stromal cell populations used for comparison differed in their ability to promote *osteoclast*-like multinucleated cell (OCL) formation. mRNA for *IL*-*18* was found to be expressed in greater abundance in lines that were unable to support OCL formation than in supportive cells. Recombinant *IL*-*18* was found to inhibit OCL formation in cocultures of osteoblasts and hemopoietic cells of spleen or bone marrow origin. *IL*-*18* inhibited OCL formation in the presence of *osteoclastogenic* agents including 1 alpha,25-dihydroxyvitamin D-3, prostaglandin E(2), parathyroid hormone, IL-1, and IL-11. The inhibitory effect of *IL*-*18* was limited to the

early phase of the cocultures, which coincides with proliferation of hemopoietic precursors. *IL*-*18* has been reported to induce interferon-gamma (IFN-gamma) and granulocyte/macrophage colony-stimulating factor (GM-CSF) production in T cells, and both agents also inhibit OCL formation in vitro. Neutralizing antibodies to GM-CSF were able to rescue *IL*-*18* inhibition of OCL formation, whereas neutralizing antibodies to IFN-gamma did not. In cocultures with osteoblasts and spleen cells from IFN-gamma receptor type II-deficient mice, *IL*-*18* was found to inhibit OCL formation, indicating that *IL*-*18* acted independently of IFN-gamma production: IFN-gamma had no effect in these cocultures. Additionally, in cocultures in which spleen cells were derived from receptor-deficient mice and osteoblasts were from wild-type mice and vice versa, we identified that the target cells for IFN-gamma inhibition of OCL formation were the hemopoietic cells. The work provides evidence that *IL*-*18* is expressed by osteoblasts and inhibits OCL formation via GM-CSF production and not via IFN-gamma production.

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?ds s1-s2;ds s4-s6

Set	Items	Description
S1	1450	((IL OR INTERLEUKIN)(W)18 OR INTERFERON(W)GAMMA(W)INDUCING-(W)FACTOR? OR IGIF?)
S2	30	S1 AND OSTEOCLAST?

Set	Items	Description
S4	120	S1 AND (BONE? OR OSTEO?)
S5	90	S4 NOT S2
S6	32	RD (unique items)

?
?
?t s2/7/1-30

2/7/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11738882 BIOSIS NO.: 199800519578
Interleukin-*18*: Perspectives on the newest interleukin.

AUTHOR: Gillespie Matthew T(a); Horwood Nicole J
AUTHOR ADDRESS: (a)St. Vincent's Inst. Med. Res. Univ. Melbourne, Dep. Med., St. Vincent's Hosp., Fitzroy, VIC 3065, Australia

JOURNAL: Cytokine & Growth Factor Reviews 9 (2):p109-116 June, 1998
ISSN: 1359-6101
DOCUMENT TYPE: Literature Review
RECORD TYPE: Citation
LANGUAGE: English

2/7/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11674818 BIOSIS NO.: 199800456549
Interleukins in the control of *osteoclast* differentiation.

AUTHOR: Martin T J; Romas E; Gillespie M T

AUTHOR ADDRESS: St. Vincent's Inst. Med. Res., 9 Princes Street, Fitzroy 3065, Victoria, Australia

JOURNAL: Critical Reviews in Eukaryotic Gene Expression 8 (2):p107-123 1998
ISSN: 1045-4403
DOCUMENT TYPE: Literature Review
RECORD TYPE: Citation
LANGUAGE: English

2/7/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11349845 BIOSIS NO.: 199800131177
Interleukin *18* inhibits *osteoclast* formation via T cell production of granulocyte macrophage colony-stimulating factor.

AUTHOR: Horwood Nicole J; Udagawa Nobuyuki; Elliott Jan; Grail Dianne; Okamura Haruki; Kurimoto Masashi; Dunn Ashley R; Martin T John; Gillespie Matthew T(a)
AUTHOR ADDRESS: (a)St. Vincent's Inst. Med. Res., 41 Victoria Parade, Fitzroy, VIC 3065, Australia

JOURNAL: Journal of Clinical Investigation 101 (3):p595-603 Feb. 1, 1998
ISSN: 0021-9738
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: *IL*-*18* inhibits *osteoclast* (OCL) formation in vitro independent of IFN-gamma production, and this was abolished by the addition of neutralizing antibodies to GM-CSF. We now establish that *IL* -*18* was unable to inhibit OCL formation in cocultures using GM-CSF-deficient mice (GM-CSF -/-). Reciprocal cocultures using either wild-type osteoblasts with GM-CSF -/- spleen cells or GM-CSF -/- osteoblasts with wild-type spleen cells were examined. Wild-type spleen cells were required to elicit a response to *IL*-*18* indicating that cells of splenic origin were the *IL*-*18* target. As T cells comprise a large proportion of the spleen cell population, the role of T cells in *osteoclastogenesis* was examined. Total T cells were removed and repleted in various combinations. Addition of wild-type T cells to a GM-CSF -/- coculture restored *IL*-*18* inhibition of *osteoclastogenesis*. Major subsets of T cells, CD4+ and CD8+, were also individually depleted. Addition of either CD4+ or CD8+ wild-type T cells restored *IL*-*18* action in a GM-CSF -/- background, while *IL*-*18* was ineffective when either CD4+ or CD8+ GM-CSF -/- T cells were added to a wild-type coculture. These results highlight the involvement of T cells in *IL*-*18*-induced OCL inhibition and provide evidence for a new OCL inhibitory pathway whereby *IL*-*18* inhibits OCL formation due to action upon T cells promoting the release of GM-CSF, which in turn acts upon OCL recursors.

2/7/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10882805 BIOSIS NO.: 199799503950

Interleukin-*18* (*interferon*-*gamma*-*inducing* *factor*) is produced by osteoblasts and acts via granulocyte/macrophage colony-stimulating factor and not via interferon-gamma to inhibit *osteoclast* formation.

AUTHOR: Udagawa Nobuyuki; Horwood Nicole J; Elliot Jan; Mackay Alan; Owens Jane; Okamura Haruki; Kurimoto Masashi; Chambers Timothy J; Martin T John ; Gillespie Matthew T(a)
AUTHOR ADDRESS: (a)St. Vincent's Inst. Medical Research, 41 Victoria Parade, Fitzroy 3065, Vic, Australia

JOURNAL: Journal of Experimental Medicine 185 (6):p1005-1012 1997
ISSN: 0022-1007
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We have established by differential display polymerase chain reaction of mRNA that interleukin (*IL*)-*18* is expressed by osteoblastic stromal cells. The stromal cell populations used for comparison differed in their ability to promote *osteoclast*-like multinucleated cell (OCL) formation. mRNA for *IL*-*18* was found to be expressed in greater abundance in lines that were unable to support OCL formation than in supportive cells. Recombinant *IL*-*18* was found to inhibit OCL formation in cocultures of osteoblasts and hemopoietic cells of spleen or bone marrow origin. *IL*-*18* inhibited OCL formation in the presence of *osteoclastogenic* agents including 1-alpha,25-dihydroxyvitamin D-3, prostaglandin E-2, parathyroid hormone, IL- 1, and IL-11. The inhibitory effect of *IL*-*18* was limited to the early phase of the cocultures, which coincides with proliferation of hemopoietic precursors. *IL*-*18* has been reported to induce interferon-gamma (IFN-gamma) and granulocyte/macrophage colony-stimulating factor (GM-CSF) production in T cells, and both agents also inhibit OCL formation in vitro. Neutralizing antibodies to GM-CSF were able to rescue *IL*-*18* inhibition of OCL formation, whereas neutralizing antibodies to IFN-gamma did not. In cocultures with osteoblasts and spleen cells from IFN-gamma receptor type II-deficient mice, *IL*-*18* was found to inhibit OCL formation, indicating that *IL*-*18* acted independently of IFN-gamma production: IFN-gamma had no effect in these cocultures. Additionally, in cocultures in which spleen cells were derived from receptor-deficient mice and osteoblasts were from wild-type mice and vice versa, we identified that the target cells for IFN-gamma inhibition of OCL formation were the hemopoietic cells. The work provides evidence that *IL*-*18* is expressed by osteoblasts and inhibits OCL formation via GM-CSF production and not via IFN-gamma production.

2/7/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

06254127 BIOSIS NO.: 000086088310
TRANSFORMING GROWTH FACTOR BETA INHIBITS BONE RESORPTION IN FETAL RAT LONG BONE CULTURES

AUTHOR: PFEILSCHIFTER J; SEYEDIN S M; MUNDY G R
AUTHOR ADDRESS: DIV. ENDOCRINOL. AND METABOLISM, UNIV. TEXAS HEALTH SCI. CENT. SAN ANTONIO, 7703 FLOYD CURL DRIVE, SAN ANTONIO, TEX. 78284-7877.

JOURNAL: J CLIN INVEST 82 (2). 1988. 680-685.
FULL JOURNAL NAME: Journal of Clinical Investigation

CODEN: JCINA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: TGF-.beta.1 is a polypeptide that is abundant in bone matrix, is produced by bone cells, and modulates proliferation and differentiated functions of osteoblastic cells in vitro. TGF-.beta.2 is a closely related polypeptide that was originally isolated from bone matrix. TGF-.beta.1 has been shown previously to stimulate prostaglandin production in cultures of neonatal mouse calvariae, which causes these bones to resorb. We found similar effects with TGF-.beta.2. In comparison, TGF-.beta.1 and TGF-.beta.2 failed to stimulate bone resorption in fetal rat long bone cultures during a 3-d incubation period in concentrations up to 50-100 times greater than those capable of inducing bone resorption in calvariae. Incubation with TGF-.beta.1 for a further 3 d decreased bone resorption up to 30%. Moreover, bone resorption induced by the bone-resorbing agents IL 1 and 1,25-dihyroxyvitamin D3 was partially or completely inhibited by TGF-.beta.1 and TGF-.beta.2 during the second half of the 6-d incubation period. Inhibition of DNA synthesis with hydroxyurea inhibited bone resorption in long bones in a similar pattern to that seen with TGF-.beta.1. The inhibitory effects of TGF-.beta.1 and TGF-.beta.2 on bone resorption in long bone cultures may therefore be due to inhibition of *osteoclast* precursor proliferation.

2/7/6 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

06971963 Genuine Article#: 110EV Number of References: 143
Title: Interleukins in the control of *osteoclast* differentiation
Author(s): Martin TJ; Romas E; Gillespie MT
Corporate Source: ST VINCENTS INST MED RES,/FITZROY/VIC 3065/AUSTRALIA/
Journal: CRITICAL REVIEWS IN EUKARYOTIC GENE EXPRESSION, 1998, V8, N2, P 107-123
ISSN: 1045-4403 Publication date: 19980000
Publisher: BEGELL HOUSE INC, 79 MADISON AVE, SUITE 1205, NEW YORK, NY 10016-7892
Language: English Document Type: REVIEW
Abstract: To maintain homeostasis of bone, the production of osteoblasts and *osteoclasts* is tightly regulated. At the local level, hormones and cytokines control formation of *osteoclasts* from hemopoietic precursors by acting upon osteoblastic-stromal cells and in some cases also upon cells of the immune system. Osteoblasts regulate *osteoclast* formation by providing physical support and cytokines such as M-CSF and IL-11, which promote *osteoclast* differentiation. Osteoblasts are also a source of *IL*-*18*, which limits *osteoclast* formation. The require ment of contact between osteoblasts and hemopoietic cells for successful *osteoclast* formation led to a concept of a membrane-anchored stromal cell molecule that programs *osteoclast* differentiation. This mechanism has been highlighted by the discovery of osteoprotegerin (OPG), a soluble tumor necrosis factor (TNF) family member that inhibits *osteoclast* formation. The ligand for OPG is a novel transmembrane TNF receptor superfamily member, the *osteoclast* differentiating factor (ODF). The recognition of the osteoprotegerin/osteoprotegerin-ligand axis will lead to new insights into the control of *osteoclast* differentiation by interleukins.

2/7/7 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

06480038 Genuine Article#: YW195 Number of References: 25
Title: *Interleukin* *18* inhibits *osteoclast* formation via T cell production of granulocyte macrophage colony-stimulating factor
Author(s): Horwood NJ; Udagawa N; Elliott J; Grail D; Okamura H; Kurimoto M ; Dunn AR; Martin TJ; Gillespie MT (REPRINT)
Corporate Source: ST VINCENTS INST MED RES,41 VICTORIA PARADE/FITZROY/VIC 3065/AUSTRALIA/ (REPRINT); ST VINCENTS INST MED RES,/FITZROY/VIC 3065/AUSTRALIA/; UNIV MELBOURNE,ST VINCENTS HOSP, DEPT MED/FITZROY/VIC 3065/AUSTRALIA/; SHOWA UNIV,SCH DENT, DEPT BIOCHEM/TOKYO 142//JAPAN/; LUDWIG INST CANC RES,/PARKVILLE/VIC 3052/AUSTRALIA/; HYOGO MED UNIV,DEPT IMMUNOL & MED ZOOL/NISHINOMIYA/HYOGO 663/JAPAN/; HAYASHIBARA BIOCHEM LABS INC,FUJISAKI INST/OKAYAMA 702//JAPAN/
Journal: JOURNAL OF CLINICAL INVESTIGATION, 1998, V101, N3 (FEB 1), P 595-603
ISSN: 0021-9738 Publication date: 19980201
Publisher: ROCKEFELLER UNIV PRESS, 1114 FIRST AVE, 4TH FL, NEW YORK, NY 10021
Language: English Document Type: ARTICLE
Abstract: *IL*-*18* inhibits *osteoclast* (OCL) formation in vitro independent of IFN-gamma production, and this was abolished by the addition of neutralizing antibodies to GM-CSF, We now establish that *IL*-*18* was unable to inhibit OCL formation in cocultures using GM-CSF-deficient mice (GM-CSF -/-). Reciprocal cocultures using either wild-type osteoblasts with GM-CSF -/- spleen cells or GM-CSF -/- osteoblasts with wild-type spleen cells were examined. Wild-type spleen cells were required to elicit a response to *IL*-*18* indicating that cells of splenic origin were the *IL*-*18* target. As T cells comprise a large proportion of the spleen cell population, the role of T cells in *osteoclastogenesis* was examined. Total T cells were removed and repleted in various combinations, Addition of wild-type T cells to a GM-CSF -/- coculture restored *IL*-*18* inhibition of *osteoclastogenesis*, Major subsets of T cells, CD4(+) and CD8(+), were also individually depleted, Addition of either CD4(+) or CD8(+) wildtype T cells restored *IL*-*18* action in a GM-CSF -/- background, while *IL*-*18* was ineffective when either CD4(+) or CD8(+) GM-CSF -/- T cells were added to a wild-type coculture. These results highlight the involvement of T cells in *IL*-*18*-induced OCL inhibition and provide evidence for a new OCL inhibitory pathway whereby *IL*-*18* inhibits OCL formation due to action upon T cells promoting the release of GM-CSF, which in turn acts upon OCL precursors.

2/7/8 (Item 3 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

06104525 Genuine Article#: XP627 Number of References: 0
Title: *Interleukin*-*18* inhibits *osteoclast* formation via T-cell production of GM-CSF.
Author(s): Horwood NJ; Udagawa N; Elliott I; Okamura H; Kurimoto M; Dunn A; Chambers TJ; Martin TJ; Gillespie MT
Corporate Source: ST VINCENTS INST MED RES,/FITZROY/VIC 3065/AUSTRALIA/; HYOGO MED UNIV,DEPT BACTERIOL/NISHINOMIYA/HYOGO/JAPAN/; FUJISAKI INST,/OKAYAMA//JAPAN/; LUDWIG INST,/MELBOURNE/VIC/AUSTRALIA/; UNIV LONDON ST GEORGES HOSP,SCH MED, DEPT HISTOPATHOL/LONDON//ENGLAND/
Journal: JOURNAL OF BONE AND MINERAL RESEARCH, 1997, V12, 1 (AUG), P183-183

ISSN: 0884-0431 Publication date: 19970800
Publisher: BLACKWELL SCIENCE INC, 350 MAIN ST, MALDEN, MA 02148
Language: English Document Type: MEETING ABSTRACT

2/7/9 (Item 4 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

05672761 Genuine Article#: WP404 Number of References: 39
Title: *Interleukin*-*18* (*interferon*-*gamma*-*inducing* *factor*) is
produced by osteoblasts and acts via granulocyte/macrophage
colony-stimulating factor and not via interferon-gamma to inhibit
osteoclast formation
Author(s): Udagawa N; Horwood NJ; Elliott J; Mackay A; Owens J; Okamura H;
Kurimoto M; Chambers TJ; Martin TJ; Gillespie MT (REPRINT)
Corporate Source: ST VINCENTS INST MED RES,41 VICTORIA PARADE/FITZROY/VIC
3065/AUSTRALIA/ (REPRINT); ST VINCENTS INST MED RES,/FITZROY/VIC
3065/AUSTRALIA/; UNIV MELBOURNE,ST VINCENTS HOSP, DEPT MED/FITZROY/VIC
3065/AUSTRALIA/; ST GEORGE HOSP,SCH MED, DEPT HISTOPATHOL/LONDON SW17
0RE//ENGLAND/; HYOGO MED UNIV,DEPT BACTERIOL/NISHINOMIYA/HYOGO
663/JAPAN/; HAYASHIBARA BIOCHEM LABS INC,FUJISAKI INST/OKAYAMA
702//JAPAN/
Journal: JOURNAL OF EXPERIMENTAL MEDICINE, 1997, V185, N6 (MAR 17), P
1005-1012
ISSN: 0022-1007 Publication date: 19970317
Publisher: ROCKEFELLER UNIV PRESS, 1114 FIRST AVE, 4TH FL, NEW YORK, NY
10021
Language: English Document Type: ARTICLE
Abstract: We have established by differential display polymerase chain
reaction of mRNA that interleukin (*IL*)-*18* is expressed by
osteoblastic stromal cells. The stromal cell populations used for
comparison differed in their ability to promote *osteoclast*-like
multinucleated cell (OCL) formation. mRNA for *IL*-*18* was found to be
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formation than in supportive cells. Recombinant *IL*-*18* was found to
inhibit OCL formation in cocultures of osteoblasts and hemopoietic
cells of spleen or bone marrow origin. *IL*-*18* inhibited OCL
formation in the presence of *osteoclastogenic* agents including 1
alpha,25-dihydroxyvitamin D-3, prostaglandin E(2), parathyroid hormone,
IL-1, and IL-11. The inhibitory effect of *IL*-*18* was limited to the
early phase of the cocultures, which coincides with proliferation of
hemopoietic precursors. *IL*-*18* has been reported to induce
interferon-gamma (IFN-gamma) and granulocyte/macrophage
colony-stimulating factor (GM-CSF) production in T cells, and both
agents also inhibit OCL formation in vitro. Neutralizing antibodies to
GM-CSF were able to rescue *IL*-*18* inhibition of OCL formation,
whereas neutralizing antibodies to IFN-gamma did not. In cocultures
with osteoblasts and spleen cells from IFN-gamma receptor type
II-deficient mice, *IL*-*18* was found to inhibit OCL formation,
indicating that *IL*-*18* acted independently of IFN-gamma production:
IFN-gamma had no effect in these cocultures. Additionally, in
cocultures in which spleen cells were derived from receptor-deficient
mice and osteoblasts were from wild-type mice and vice versa, we
identified that the target cells for IFN-gamma inhibition of OCL
formation were the hemopoietic cells. The work provides evidence that
IL-*18* is expressed by osteoblasts and inhibits OCL formation via
GM-CSF production and not via IFN-gamma production.

ISHER: Rockefeller University Press
UMENT TYPE: Journal
NGUAGE: English

AB IL-18 inhibits osteoclast (OCL) formation in vitro independent of IFN-.gamma. prodn., and this was abolished by the addn. of neutralizing antibodies to GM-CSF. The authors now establish that IL-18 was unable to inhibit OCL formation in cocultures using GM-CSF-deficient mice (GM-CSF -/-). Reciprocal cocultures using either wild-type osteoblasts with GM-CSF -/- spleen cells or GM-CSF -/- osteoblasts with wild-type spleen cells were examd. Wild-type spleen cells were required to elicit a response to IL-18 indicating that cells of splenic origin were the IL-18 target. As T cells comprise a large proportion of the spleen cell population, the role of T cells in osteoclastogenesis was examd. Total T cells were removed and repleted in various combinations. Addn. of wild-type T cells to a GM-CSF -/- coculture restored IL-18 inhibition of osteoclastogenesis. Major subsets of T cells, CD4+ and CD8+, were also individually depleted. Addn. of either CD4+ or CD8+ wild-type T cells restored IL-18 action in a GM-CSF -/- background, while IL-18 was ineffective when either CD4+ or CD8+ GM-CSF -/- T cells were added to a wild-type coculture. These results highlight the involvement of T cells in IL-18-induced OCL inhibition and provide evidence for a new OCL inhibitory pathway whereby IL-18 inhibits OCL formation due to action upon T cells promoting the release of GM-CSF, which in turn acts upon OCL precursors.

L5 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 1999 ACS

ACCESSION NUMBER: 1997:192313 HCAPLUS
DOCUMENT NUMBER: 126:262973

TITLE: **Interleukin-18 (interferon-.gamma.-inducing factor**) is produced by osteoblasts and acts via granulocyte/macrophage colony-stimulating factor and not via interferon-.gamma. to inhibit **osteoclast** formation

AUTHOR(S): Udagawa, Nobuyuki; Horwood, Nicole J.; Elliott, Jan; Mackay, Alan; Owens, Jane; Okamura, Haruki; Kurimoto, Masahi; Chambers, Timothy J.; Martin, T. John; Gillespie, Matthew T.
CORPORATE SOURCE: St. Vincent's Institute Medical Research, University Melbourne, Fitzroy, 3065, Australia

SOURCE: J. Exp. Med. (1997), 185(6), 1005-1012
CODEN: JEMEAV; ISSN: 0022-1007
PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We have established by differential display polymerase chain reaction of mRNA that interleukin (**IL**)-**18** is expressed by osteoblastic stromal cells. The stromal cell populations used for comparison differed in their ability to promote **osteoclast**-like multinucleated cell (OCL) formation. MRNA for **IL-18** was found to be expressed in greater abundance in lines that were unable to support OCL formation than in supportive cells. Recombinant **IL-18** was found to inhibit OCL formation in cocultures of osteoblasts and hemopoietic cells of spleen or bone marrow origin. **IL-18** inhibited OCL formation in the presence of **osteoclastogenic** agents including 1.alpha.,25-dihydroxyvitamin D3, prostaglandin E2, parathyroid hormone, IL-1, and IL-11. The inhibitory effect of **IL-18** was limited to the early phase of the cocultures, which coincides with proliferation of hemopoietic precursors. **IL-18** has been reported to induce interferon-.gamma. (IFN-.gamma.) and granulocyte/macrophage colony-stimulating factor (GM-CSF) prodn. in T cells, and both agents also inhibit OCL formation in vitro. Neutralizing antibodies to GM-CSF were able to rescue **IL-18** inhibition of OCL formation, whereas neutralizing antibodies

to IFN-.gamma. did not. In cocultures with osteoblasts and spleen cells from IFN-.gamma. receptor type II-deficient mice, **IL-18** was found to inhibit OCL formation, indicating that **IL-18** acted independently of IFN-.gamma. prodn.: IFN-.gamma. had no effect in these cocultures. Addnl., in cocultures in which spleen cells were derived from receptor-deficient mice and osteoblasts were from wild-type mice and vice versa, we identified that the target cells for IFN-.gamma. inhibition of OCL formation were the hemopoietic cells. This work provides evidence that **IL-18** is expressed by osteoblasts and inhibits OCL formation via GM-CSF prodn. and not via IFN-.gamma. prodn.

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2/7/10 (Item 1 from file: 47)
DIALOG(R)File 47:Magazine Database(TM)

04689824 SUPPLIER NUMBER: 19061126 (THIS IS THE FULL TEXT)
Activation of *interferon*-*gamma* *inducing* *factor* mediated by interleukin-1 beta converting enzyme.
Gu, Yong; Kuida, Keisuke; Tsutsui, Hiroko; Ku, George; Hsiao, Kathy; Fleming, Mark A.; Hayashi, Nobuki; Higashino, Kazuya; Okamura, Haruki; Nakanishi, Kenji; Kurimoto, Masashi; Tanimoto, Tadao; Flavell, Richard A.; Sato, Vicki; Harding, Matthew; Livingston, David J.; Su, Michael S.-S.
Science, v275, n5297, p206(3)
Jan 10, 1997

TEXT:

ICE is a member of the growing family of ICE-like cysteine proteases (caspases) with a substrate specificity for aspartate (1). ICE (caspase-1) was identified on the basis of its proteolytic activity for cleaving the inactive IL-1(beta) precursor into the 17-kD mature cytokine (2). ICE-deficient mice are impaired in their production of mature IL-1(beta) (3), which establishes the physiological role of ICE in the processing and export of IL-1(beta). In contrast to IL-1(beta)-deficient mice (4), (ICE.sup.-/-) mice also have less IL-1(alpha), tumor necrosis factor-(alpha) (TNF-(alpha)), and IL-6 and are resistant to septic shock induced by endotoxin (3), which suggests that ICE may have additional functions in the regulation of the immune system.

IGIF, an ~18-kD polypeptide that stimulates production of interferon-(gamma) (IFN-(gamma)) by T cells (5), is synthesized as a polypeptide precursor (proIGIF) devoid of a conventional signal sequence (6). The precursor of *IGIF* is cleaved after (Asp.sup.35) (6), which suggests that an aspartate-specific protease may be involved. Two families of proteases with substrate specificity for aspartate have been identified; these include the ICE family of cysteine proteases and granzyme B, a serine protease involved in cytotoxic lymphocyte-mediated cell killing and activation of ICE-like cysteine proteases (7, 8). Therefore, we investigated whether one or more of the ICE-family proteases or granzyme B may be involved in the processing of proIGIF and investigated the role that such a cleavage may have in the function of *IGIF*.

We first used transient coexpression in COS cells (9) to determine whether proIGIF could be processed by some of the known ICE-family proteases (Fig. 1A). Coexpression of proIGIF with ICE or its homolog TX (caspase-4) (10) resulted in the cleavage of proIGIF into a polypeptide similar in size to the naturally occurring 18-kD *IGIF*. Single point mutations of the catalytic cysteine residues that inactivate ICE and TX (11) blocked cleavage. Coexpression with CPP32 (caspase-3), a protease involved in programmed cell death (apoptosis) (12), resulted in the cleavage of proIGIF into a ~14-kD polypeptide, whereas CMH-1 (caspase-7), a homolog of CPP32 (13), did not appreciably cleave proIGIF. Thus, ICE and TX could cleave proIGIF into a polypeptide similar to the naturally occurring *IGIF*.

We examined the cleavage of proIGIF by these proteases in vitro with the use of purified recombinant ((His).sub.6)-tagged proIGIF as a substrate (14). ICE cleaved the 24-kD proIGIF into two polypeptides of ~18 and ~6 kD (Fig. 1B). The 18-kD polypeptide comigrated with recombinant mature *IGIF* upon SDS-polyacrylamide gel electrophoresis (PAGE) and contained the same amino acid residues (Asn-Phe-Gly-Arg-Leu) at its N(H.sub.2)-terminus as did the naturally occurring murine *IGIF*, indicating that ICE cleaved proIGIF at the authentic processing site ((Asp.sup.35-(Asn.sup.36)) (6). This cleavage was specific with a catalytic efficiency ((k.sub.cat)/(K.sub.m), where (K.sub.m) is the Michaelis constant) of 1.4 x (10.sup.7) (M.sup.-1)

(s.sup.-1) ((K.sub.m) = 0.6 (+ or -) 0.1 (mu)M; (k.sub.cat) = 8.6 (+ or -) 0.3 (s.sup.-1)) (15) and was inhibited by the specific ICE inhibitors Ac-Tyr-Val-Ala-Asp-aldehyde (2) and Cbz-Val-Ala-Asp-((2,6-dichlorobenzoyl)oxy)methyl ketone (16). Recombinant ((His).sub.6)-tagged human proIGIF was also cleaved by ICE with a similar specificity. Although proIGIF had no detectable IFN-(gamma)-inducing activity, ICE-cleaved proIGIF was active in inducing IFN-(gamma) production in T helper type 1 ((T.sub.H)1) cells (Fig. 1C) (17). TX also cleaved proIGIF into polypeptides of similar size; however, its catalytic efficiency was about two orders of magnitude lower than that of ICE. In a manner consistent with the observation from the COS cell experiments, CPP32 cleaved proIGIF at a different site ((Asp.sup.69)-(Ile.sup.70)) and the resulting polypeptides had little IFN-(gamma)-inducing activity, whereas CMH-1 and granzyme B did not cleave proIGIF. Thus, both in COS cells and in vitro, ICE can process the inactive *IGIF* precursor at the authentic maturation site to generate the biologically active form of *IGIF*.

IGIF is produced by activated Kupffer cells and macrophages in vivo and is exported from the cells upon stimulation by endotoxin (5, 6). We used the COS cell coexpression system to investigate whether the cleavage of proIGIF by ICE would facilitate the export of mature *IGIF*, as in the case of IL-(beta) (2). COS cells coexpressing proIGIF and ICE were labeled with ((sub.35)S)methionine (18). COS cell lysates and conditioned medium were immunoprecipitated with an antiserum to *IGIF* that recognizes both the precursor and the mature form (6) (Fig. 2A). An 18-kD polypeptide corresponding to the mature *IGIF* was detected in the conditioned medium of COS cells coexpressing proIGIF and ICE, whereas COS cells expressing proIGIF alone or with the inactive ICE mutant exported only a very small amount of proIGIF. We estimated by PhosphorImager analysis that $\sim 10\%$ of the mature *IGIF* was exported from transfected cells, whereas $< 1\%$ of proIGIF was exported. We also measured the presence of IFN-(gamma)-inducing activity in cell lysates and in the conditioned media of transfected cells (19). IFN-(gamma)-inducing activity was detected in both cell lysates and conditioned medium of COS cells coexpressing proIGIF and ICE, but not those of cells expressing proIGIF or ICE alone (Fig. 2B). The relative amounts of mature *IGIF* in the medium and in cell lysates (19) indicated that the secreted *IGIF* was at least as active as the cytosolic mature *IGIF*. Thus, ICE cleavage of proIGIF can facilitate the export of mature and active *IGIF* from cells.

To study the role of ICE in the activation and export of *IGIF* under physiological conditions, we examined the processing and export of *IGIF* from lipopolysaccharide (LPS)-stimulated Kupffer cells isolated from Propionibacterium acnes-elicited wild-type and (ICE.sup.-/-) mice (20). Although lysates of Kupffer cells from wild-type and (ICE.sup.-/-) mice contained similar amounts of *IGIF* (as determined by an enzyme-linked immunosorbent assay (ELISA) that recognized both proIGIF and mature *IGIF*), *IGIF* was detected in the conditioned medium of wild-type cells but not in that of (ICE.sup.-/-) cells (Fig. 3A). Metabolic labeling and immunoprecipitation experiments confirmed the presence of unprocessed proIGIF in both wild-type and (ICE.sup.-/-) Kupffer cell lysates. However, the 18-kD mature *IGIF* was present only in the conditioned medium of wild-type Kupffer cell cultures and not in that of (ICE.sup.-/-) cultures (Fig. 3B). Similarly, the conditioned medium of LPS-stimulated wild- type adherent splenocytes contained IFN-(gamma)-inducing activity that was sensitive to a neutralizing antibody to *IGIF* (anti-*IGIF*); this activity was reduced in the medium of adherent splenocytes of (ICE.sup.-/-) mice (Fig. 3C). The absence of *IGIF* in the conditioned medium of (ICE.sup.-/-) Kupffer cells and adherent splenocytes established that the processing of proIGIF by ICE is required for the export of *IGIF*.

The sera of (ICE.sup.-/-) mice stimulated by P. acnes and LPS (21) also contained reduced amounts of *IGIF* (Fig. 4A). This finding may

account for the lower concentrations of IFN-(gamma) in the sera of treated (ICE.sup.-/-) mice (Fig. 4B) (22) because we observed no difference between wild-type and (ICE.sup.-/-) mice in the production of IL-12, the other cytokine known to induce IFN-(gamma) (23). Nonadherent splenocytes from wild-type and (ICE.sup.-/-) mice produced similar amounts of IFN-(gamma) when stimulated with *IGIF* in vitro. Administration of recombinant mature *IGIF* (6) into (ICE.sup.-/-) mice restored IFN-(gamma) production in these animals (Fig. 4B) which indicated that the impaired production of IFN-(gamma) was not the result of a defect in the T cells of (ICE.sup.-/-) mice. Moreover, injection of neutralizing anti-*IGIF* suppressed IFN-(gamma) production in wild-type animals stimulated by P. acnes and LPS (Fig. 4C). The defect in IFN-(gamma) production in (ICE.sup.-/-) mice was comparable in magnitude to the defect in IL-1(beta) release, whereas only slight reductions were observed for TNF-(alpha) or IL-6 (3). Thus, ICE is necessary for processing of the *IGIF* precursor and export of active *IGIF*.

IFN-(gamma) and IL-1(beta) are pleiotropic cytokines that contribute to the pathology associated with a variety of infectious, inflammatory, and autoimmune diseases. IFN-(gamma) promotes the activation of macrophages and natural killer cells and contributes to the regulation of T helper cell immune responses, whereas IL-1(beta) stimulates proinflammatory responses in neutrophils, endothelial cells, synovial cells, *osteoclasts*, and other cell types (24). The processing of proIGIF by ICE establishes a link in the regulation of IL-1(beta) and IFN-(gamma) production with implications for monocyte- or macrophage-mediated and T cell-mediated immune functions. IFN-(gamma) can increase the expression of ICE in monocytic cells (25), which suggests a positive-feedback regulation between ICE and IFN-(gamma) that may further enhance the production of *IGIF* and IL-1(beta). However, IFN-(gamma) production by antigen-specific T cells may not be dependent on the ICE-TGIF pathway, because mitogen (concanavalin A) or antigen stimulation of splenic T cells from (ICE.sup.-/-) mice elicited release of normal amounts of IFN-(gamma) (26). T cell proliferation and delayed-type hypersensitivity responses are normal in (ICE.sup.-/-) mice after a secondary exposure to Listeria monocytogenes (22). Thus, the ICE-TGIF pathway of IFN-(gamma) production may be more relevant in vivo to monocyte- or macrophage-mediated inflammatory insults, as opposed to T cell-dependent immune responses.

ICE processing of proIGIF and IFN-(gamma) production may be central events in the pathogenesis of sepsis. Mice lacking IFN-(gamma) or its receptor are resistant to endotoxic shock (27), and neutralizing anti-*IGIF* prevents LPS-induced hepatic injury in P. acres-primed mice (6). These observations suggest that the reduced concentrations of IL-1(beta), *IGIF*, and IFN-(gamma) in LPS-exposed (ICE.sup.-/-) mice (3, 22) account for their increased resistance to LPS-induced sepsis relative to mice lacking a functional IL-1(beta) gene (4), which have a normal septic response. The involvement of ICE in the regulation of these multiple proinflammatory cytokines should be considered in future evaluations of the therapeutic effects of ICE inhibition.

(Figures 1 to 4 ILLUSTRATIONS OMITTED)

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encoding full-length murine proIGIF (6) was ligated into the mammalian expression vector pCDLSR(alpha) (23). Plasmids for the expression of active human ICE (11), TX (10), and CMH-1 (13) lacking the prosequence were as described. Expression plasmid for the active form of CPP32 lacking the proseqUenCe (12) was constructed similarly in the pCDLSR(alpha) vector. Plasmids (3 (mu)g) were transfected into COS cells in 35-mm dishes by the DEAE-dextran method (11). Twenty-four hours later, cells were lysed and the lysates were subjected to SDS-PAGE and immunoblotting with an antiserum to *IGIF* (6). (10.) C. Faucheu et al., EMBO J. 14, 1914 (1995). (11.) Y. Gu et al., ibid., p. 1923. (12.) T. Fernandes-Alnemri, G. Litwack, E. S. Alnemri, J. Biol. Chem. 269,30761 (1994); D. W. Nicholson et al., Nature 376, 37 (1995); M. Tewari et al., Cell 81, 801 (1995). (13.) J. A. Lippke, Y. Gu, C. Sarnecki, P. R. Caron, M. S.-S. Su, J. Biol. Chem. 271, 1825 (1996). (14.) Expression plasmid for ((His).sub.6)-proIGIF was created by introducing Nde I sites at the ends of murine proIGIF cDNA coding sequence (6) and ligating into Escherichia cold expression vector pET-15B (Novagen). The E. cold strain BL21 (DE3) carrying the plasmid was induced with isopropyl-1 -thio-(beta)-D-galactopyranoside. ((His).sub.6)-proIGIF protein was purified from soluble fractions by Ni-nitrilotriacetic acid-agarose (Qiagen) chromatography according to the manufacturer's instructions. In vitro cleavage reactions by ICE and ICE-like proteases were carried out as in (29). Conditions for cleavage by granzyme B were as in (8). Cleavage products were analyzed by SDS-PAGE on 16% gels and Coomassie blue staining and were subjected to N(H.sub.2)-terminal amino acid sequencing with an ABI automated peptide sequencer. (15.) ((sup.35)S)methionine-labeled proIGIF (~3000 cpm, prepared by in vitro transcription and translation with the TNT T7 coupled reticulocyte lysate system (Promega) and proIGIF cDNA in pSP73 vector as template) was incubated in reaction mixtures of 60 (mu)l containing 0.1 to 1 nM recombinant ICE and 190 nM to 12 (mu)M unlabeled proIGIF for 8 to 10 min at 37(degrees) C. Cleavage product concentrations were determined by SDS-PAGE and PhosphorImager analysis. The kinetic parameters were calculated by nonlinear regression fitting of the rate versus concentration data to the Michaelis-Menten equation by means of the program Enzfitter (Biosoft). (16.) R. E. Dolle et al., J. Med. Chem. 37, 563 (1994). (17.) The (T.sub.H)1 A. E7 cells (30) (1.3 x (10.sup.5) cells in O.15 ml) or nonadherent splenic T cells (8 x (10.sup.5) cells) in 96-well plates were treated with *IGIF* or conditioned medium for 18 to 20 hours, and the culture supernatants were assayed for IFN-(gamma) by ELISA (Endogen, Cambridge, MA). (18.) COS cells (3.5 x (10.sup.5) cells in a 35-mm dish) were labeled for 7 hours with 1 ml of methionine-free Dulbecco's modified Eagle's medium (DMEM) containing 2.5% normal DMEM, 1% dialyzed fetal bovine serum (FBS), and (sup.35)S)methionine (300 (mu)Ci/ml; ((sup.35)S)Express Protein Labeling Mix, New England Nuclear). Cell lysates (prepared in 20 mM Hepes (pH 7.2), 150 mM NaCl, 0.1 % Triton X- 100, 5 mM N-ethylmaleimide, 1 mM phenylmethylsulfonyl fluoride, and leupeptin (2.5 (mu)g/ml)) or conditioned medium were immunoprecipitated with the antiserum to *IGIF* (6). (19.) COS cells (3.5 x (10.sup.5) cells in a 35-mm dish) were transfected and grown in 1 ml of medium for 18 hours. Medium was harvested and used at 1 :10 final dilution in the IFN-(gamma) induction assay (17); COS cell pellets from the same transfection were lysed in 100 (mu)l of 20 mM Hepes (pH 7.0) by three cycles of freezing and thawing. Lysates were cleared by centrifugation and were used at 1 :10 dilution in the assay. On the basis of our analysis that 10% mature *IGIF* was exported out of the cells, we estimated that the mature *IGIF* concentration in lysates is ~90 times that of the conditioned medium. (20.) Wild-type or ICE-deficient mice were injected intraperitoneally with 1 mg of heat-killed P. acnes (5). Kupffer cells were prepared 7 days later (31), except that nycodenz gradient was used instead of metrizamide. For each experiment, Kupffer cells (1 x (10.sup.6) cells per milliliter) from two or three animals were pooled and cultured in RPMI 1640 supplemented with 10% FBS and

LPS (1 (mu)g/ml; Difco, E. cold strain 055:B5). Cell lysates and conditioned media were prepared 3 hours later. *IGIF* was determined by ELISA with protein G-purified rabbit polyclonal antibody to murine *IGIF* (6). Metabolic labeling and immunoprecipitation experiments were carried out as for COS cells (18) except that methionine-free RPMI 1640 was used in place of DMEM. To prepare conditioned medium of LPS-stimulated adherent splenocytes, we cultured total splenic cells (6 x (10.sup.7) cells in 1 ml) from wild-type or (ICE.sup.-/-) mice for 1 hour. Adherent cells were then stimulated with LPS (50 ng/ml) for 5 hours. Conditioned media were harvested and used at 1:4 dilution in the IFN-(gamma) assay (17) in the presence or absence of anti-*IGIF* (25 (mu)g/ml) (6). (21.) Wild-type or ICE-deficient mice were primed with P. acnes (20). Seven days later, mice were exposed to LPS (1 (mu)g, intravenously). In some experiments, recombinant mature *IGIF* (1 (mu)g) or protein G-purified anti-*IGIF* (250 (mu)g) was coinjected with LPS; sera were collected 3 hours after LPS exposure. (22.) Reduced IFN-(gamma) was also observed in Listeria-infected (N. M. Tsuji et al., in preparation) and LPS-exposed (G. Ku et al., in preparation) (ICE.sup.-/-) mice. (23.) G. Trinchieri, Annul Rev. Immunol. 13, 251 (1995). (24.) F. Belardelli, APMIS 103, 161 (1995); C. A. Dinarello, Blood 87, 2095 (1996). (25.) N. Margolis and C. Dinarello, unpublished data. (26.) G. Ku and M. W. Harding, unpublished data. (27.) D. K. Dalton et al., Science 259, 1739 (1993); S. Huang et al., ibid., p. 1742; B. D. Car et al., J. Exp. Med. 179, 1437 (1994). (28.) Y. Takebe et al., Mol. Cell. Biol. 8, 466 (1988). (29.) Y. Gu, C. Sarnecki, R. A. Aldape, D. J. Livingston, M. S.-S. Su, J. Biol. Chem. 270, 18715 (1995). (30.) H. Quill and R. H. Schwartz, J. Immunol. 138, 3704 (1987). (31.) H. Tsutsui, Y. Mizoguchi, S. Morisawa, Hepato-Gastroenterology 39, 553 (1992). (32.) We thank T. Fox and W. Chen for ICE and TX protein; A. Diu, C. Faucheu and J.-L. Lalanne for TX cDNA; M. Rincon for A. E7 cells; J. Lippke for CPP32 and CMH-1 cDNA; B. O'Hare for oligonucleotide synthesis and DNA sequencing; T. Faust for ELISA; A. Heiser for animal surgery; and J. Boger for critical reading and discussion of the manuscript. R.A.F. is an HHMI Investigator.

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2/7/11 (Item 1 from file: 71)
DIALOG(R)File 71:ELSEVIER BIOBASE

00574151 97076975
Interleukin-*18* (*interferon*-*gamma*-*inducing* *factor*) is produced by osteoblasts and acts via granulocyte/macrophage colony-stimulating factor and not via interferon-gamma to inhibit *osteoclast* formation
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We have established by differential display polymerase chain reaction of mRNA that interleukin (*IL*)-*18* is expressed by osteoblastic stroma cells. The stromal cell populations used for comparison differed in their ability to promote *osteoclast*-like multinucleated cell (OCL) formation. mRNA for *IL*-*18* was found to be expressed in greater abundance in lines that were unable to support OCL formation than in supportive cells. Recombinant *IL*-*18* was found to inhibit OCL formation in cocultures of osteoblasts and hemopoietic cells of spleen or bone marrow origin. *IL*-*18* inhibited OCL formation in the presence of *osteoclastogenic* agents including, 1alpha, 25-dihydroxyvitamin Dinf 3, prostaglandin Einf 2, parathyroid hormone, IL-1, and IL-11. The inhibitory effect of *IL*-*18* was limited to the early phase of the cocultures, which coincides with proliferation of hemopoietic precursors. *IL*-*18* has been reported to induce interferon-gamma (IFN-gamma) and granulocyte/macrophage colony-stimulating factor (GM-CSF) production in T cells, and both agents also inhibit OCL formation in vitro. Neutralizing antibodies to GM-CSF were able to rescue *IL*-*18* inhibition of OCL formation, whereas neutralizing antibodies to IFN-gamma did not. It cocultures with osteoblasts and spleen cells from IFN- gamma receptor type II-deficient mice, *IL*-*18* was found to inhibit OCL formation, indicating that *IL*-*18* acted independently of IFN-gamma production; IFN-gamma had no effect in these cocultures. Additionally, in cocultures in which spleen cells were derived from receptor-deficient mice and osteoblasts were from wild- type mice and vice versa, we identified that the target cells for IFN-gamma inhibition of OCL formation were the hemepoietic cells. The work provides evidence that *IL*-*18* is expressed by osteoblasts and inhibits OCL formation via GM-CSF production and not via IFN-gamma production.

2/7/12 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

07173645 EMBASE No: 1998059693
Interleukin *18* inhibits *osteoclast* formation via T cell production of granulocyte macrophage colony-stimulating factor
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IL-*18* inhibits *osteoclast* (OCL) formation in vitro independent of

IFN- gamma production, and this was abolished by the addition of neutralizing antibodies to GM-CSF. We now establish that *IL*-*18* was unable to inhibit OCL formation in cocultures using GM-CSF-deficient mice (GM-CSF-/-). Reciprocal cocultures using either wild-type osteoblasts with GM-CSF -/- spleen cells or GM-CSF -/- osteoblasts with wild-type spleen cells were examined. Wild-type spleen cells were required to elicit a response to *IL*-*18* indicating that cells of splenic origin were the *IL* -*18* target. As T cells comprise a large proportion of the spleen cell population, the role of T cells in *osteoclastogenesis* was examined. Total T cells were removed and repleted in various combinations. Addition of wild-type T cells to a GM-CSF -/- coculture restored *IL*-*18* inhibition of *osteoclastogenesis*. Major subsets of T cells, CD4sup + and CD8sup +, were also individually depleted. Addition of either CD4sup + or CD8sup + wild-type T cells restored *IL*-*18* action in a GM-CSF -/- background, while *IL*-*18* was ineffective when either CD4sup + or CD8sup + GM-CSF -/- T cells were added to a wild-type coculture. These results highlight the involvement of T cells in *IL*-*18*-induced OCL inhibition and provide evidence for a new OCL inhibitory pathway whereby *IL*-*18* inhibits OCL formation due to action upon T cells promoting the release of GM-CSF, which in turn acts upon OCL precursors.

2/7/13 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

07120926 EMBASE No: 1998008404
Cytokines in the pathogenesis of osteoporosis
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06812899 EMBASE No: 1997095390
Interleukin-*18* (*interferon*-*gamma*-*inducing* *factor*) is produced by osteoblasts and acts via granulocyte/macrophage colony-stimulating factor and not via interferon-gamma to inhibit *osteoclast* formation
Udagawa N.; Horwood N.J.; Elliott J.; Mackay A.; Owens J.; Okamura H.; Kurimoto M.; Chambers T.J.; Martin T.J.; Gillespie M.T.
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Journal of Experimental Medicine (J. EXP. MED.) (United States) 1997,
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We have established by differential display polymerase chain reaction of mRNA that interleukin (*IL*)-*18* is expressed by osteoblastic stroma cells. The stromal cell populations used for comparison differed in their ability to promote *osteoclast*-like multinucleated cell (OCL) formation. mRNA for *IL*-*18* was found to be expressed in greater abundance in lines that were unable to support OCL formation than in supportive cells. Recombinant *IL*-*18* was found to inhibit OCL formation in cocultures of osteoblasts and hemopoietic cells of spleen or bone marrow origin. *IL*-*18* inhibited OCL formation in the presence of *osteoclastogenic* agents including, 1alpha, 25-dihydroxyvitamin Dinf 3, prostaglandin Einf 2, parathyroid hormone, IL-1, and IL-11. The inhibitory effect of *IL*-*18* was limited to the early phase of the cocultures, which coincides with proliferation of hemopoietic precursors. *IL*-*18* has been reported to induce interferon-gamma (IFN-gamma) and granulocyte/macrophage colony-stimulating factor (GM-CSF) production in T cells, and both agents also inhibit OCL formation in vitro. Neutralizing antibodies to GM-CSF were able to rescue *IL*-*18* inhibition of OCL formation, whereas neutralizing antibodies to IFN-gamma did not. It cocultures with osteoblasts and spleen cells from IFN- gamma receptor type II-deficient mice, *IL*-*18* was found to inhibit OCL formation, indicating that *IL*-*18* acted independently of IFN-gamma production; IFN-gamma had no effect in these cocultures. Additionally, in cocultures in which spleen cells were derived from receptor-deficient mice and osteoblasts were from wild- type mice and vice versa, we identified that the target cells for IFN-gamma inhibition of OCL formation were the hemepoietic cells. The work provides evidence that *IL*-*18* is expressed by osteoblasts and inhibits OCL formation via GM-CSF production and not via IFN-gamma production.

2/7/15 (Item 1 from file: 76)
DIALOG(R)File 76:Life Sciences Collection

02301532 4376053
Interleukins in the control of *osteoclast* differentiation
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To maintain homeostasis of bone, the production of osteoblasts and *osteoclasts* is tightly regulated. At the local level, hormones and cytokines control formation of *osteoclasts* from hemopoietic precursors by acting upon osteoblastic-stromal cells and in some cases also upon cells of the immune system. Osteoblasts regulate *osteoclast* formation by providing physical support and cytokines such as M-CSF and IL-11, which promote *osteoclast* differentiation. Osteoblasts are also a source of *IL*-*18*, which limits *osteoclast* formation. The requirement of contact between osteoblasts and hemopoietic cells for successful *osteoclast* formation led to a concept of a membrane-anchored stromal cell molecule that programs *osteoclast* differentiation. This mechanism has been highlighted by the discovery of osteoprotegerin (OPG), a soluble tumor necrosis factor (TNF) family member that inhibits *osteoclast* formation. The ligand for OPG is a novel transmembrane TNF receptor superfamily member, the *osteoclast* differentiating factor (ODF). The recognition of the osteoprotegerin/osteoprotegerin-ligand axis will lead to new insights into the control of *osteoclast* differentiation by interleukins.

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02281756 4329956
Interleukin *18* inhibits *osteoclast* formation via T cell production of granulocyte macrophage colony-stimulating factor
Horwood, N.J.; Udagawa, N.; Elliott, J.; Grail, D.; Okamura, H.; Kurimoto, M.; Dunn, A.R.; Martin, T.J.; Gillespie, M.T.
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DOCUMENT TYPE: Journal article LANGUAGE: ENGLISH
SUBFILE: Immunology Abstracts

IL-*18* inhibits *osteoclast* (OCL) formation in vitro independent of IFN- gamma production, and this was abolished by the addition of neutralizing antibodies to GM-CSF. We now establish that *IL*-*18* was unable to inhibit OCL formation in cocultures using GM-CSF-deficient mice (GM-CSF -/-). Reciprocal cocultures using either wild-type osteoblasts with GM-CSF -/- spleen cells or GM-CSF -/- osteoblasts with wild-type spleen cells were examined. Wild-type spleen cells were required to elicit a response to *IL*-*18* indicating that cells of splenic origin were the *IL* -*18* target. As T cells comprise a large proportion of the spleen cell population, the role of T cells in *osteoclastogenesis* was examined. Total T cells were removed and repleted in various combinations. Addition of wild-type T cells to a GM-CSF -/- coculture restored *IL*-*18* inhibition of *osteoclastogenesis*. Major subsets of T cells, CD4 super(+) and CD8 super(+), were also individually depleted. Addition of either CD4 super(+) or CD8 super(+) wild-type T cells restored *IL*-*18* action in a GM-CSF -/- background, while *IL*-*18* was ineffective when either CD4 super(+) or CD8 super(+) GM-CSF -/- T cells were added to a wild-type coculture. These results highlight the involvement of T cells in *IL*-*18*-induced OCL inhibition and provide evidence for a new OCL inhibitory pathway whereby *IL*-*18* inhibits OCL formation due to action upon T cells promoting the release of GM-CSF, which in turn acts upon OCL precursors.

2/7/17 (Item 3 from file: 76)
DIALOG(R)File 76:Life Sciences Collection

02159460 4077457
Interleukin-*18* (*interferon*- *gamma* -*inducing* *factor*) is produced by osteoblasts and acts via granulocyte/macrophage colony-stimulating factor and not via interferon- gamma to inhibit *osteoclast* formation
Udagawa, N.; Horwood, N.J.; Elliot, J.; Mackay, A.; Owens, J.; Okamura, H.; Kurimoto, M.; Chambers, T.J.; Martin, T.J.; Gillespie, M.T.
St. Vincent's Inst. Med. Res., 14 Victoria Parade, Fitzroy 3065, Vic., Australia
J. EXP. MED. vol. 185, no. 6, pp. 1005-1112 (1997)
ISSN: 0022-1007
DOCUMENT TYPE: Journal article LANGUAGE: ENGLISH
SUBFILE: Immunology Abstracts

We have established by differential display polymerase chain reaction of mRNA that interleukin (*IL*)-*18* is expressed by osteoblastic stromal

cells. The stromal cell populations used for comparison differed in their ability to promote *osteoclast*-like multinucleated cell (OCL) formation. mRNA for *IL*-*18* was found to be expressed in greater abundance in lines that were unable to support OCL formation than in supportive cells. Recombinant *IL*-*18* was found to inhibit OCL formation in cocultures of osteoblasts and hemopoietic cells of spleen or bone marrow origin. *IL*-*18* inhibited OCL formation in the presence of *osteoclastogenic* agents including 1 alpha ,25-dihydroxyvitamin D sub(3), prostaglandin E sub(2), parathyroid hormone, IL-1, and IL-11. The inhibitory effect of *IL*-*18* was limited to the early phase of the cocultures, which coincides with proliferation of hemopoietic precursors. *IL*-*18* has been reported to induce interferon- gamma (IFN- gamma) and granulocyte/macrophage colony-stimulating factor (GM-CSF) production in T cells, and both agents also inhibit OCL formation in vitro. Neutralizing antibodies to GM-CSF were able to rescue *IL*-*18* inhibition of OCL formation, whereas neutralizing antibodies to IFN- gamma did not. In cocultures with osteoblasts and spleen cells from IFN- gamma receptor type II-deficient mice, *IL*-*18* was found to inhibit OCL formation, indicating that *IL*-*18* acted independently of IFN- gamma production: IFN- gamma had no effect in these cocultures. Additionally, in cocultures in which spleen cells were derived from receptor-deficient mice and osteoblasts were from wild-type mice and vice versa, we identified that the target cells for IFN- gamma inhibition of OCL formation were the hemopoietic cells. The work provides evidence that *IL*-*18* is expressed by osteoblasts and inhibits OCL formation via GM-CSF production and not via IFN- gamma production.

2/7/18 (Item 1 from file: 94)
DIALOG(R)File 94:JICST-EPlus

04464911 JICST ACCESSION NUMBER: 98A0028829 FILE SEGMENT: JICST-E
IL-*18* (IFN-.GAMMA. inducer) directly affects *osteoclast* progenitor cells and suppresses differentiation of *osteoclasts* through GM-CSF production.
UDAGAWA NOBUYUKI (1); HORWOOD N J (1); MARTIN T J (1); GILLESPIE M T (1); SUDA TATSUO (2); KURIMOTO MASASHI (3); OKAMURA HARUKI (4); CHAMBERS T J (5)
(1) St.Vincent'sIgakuken; (2) Showa Univ., Sch. of Dent.; (3) Hayashibara Biochem. Lab., Inc.; (4)Hyogo Coll. of Med.; (5) St.George'sIgakuken
Osteoporosis Jpn, 1997, VOL.5,NO.4, PAGE.760-762, FIG.2, REF.7
JOURNAL NUMBER: L3145AAU ISSN NO: 0919-6307
UNIVERSAL DECIMAL CLASSIFICATION: 577.175.1
LANGUAGE: Japanese COUNTRY OF PUBLICATION: Japan
DOCUMENT TYPE: Journal
ARTICLE TYPE: Short Communication
MEDIA TYPE: Printed Publication

2/7/19 (Item 2 from file: 94)
DIALOG(R)File 94:JICST-EPlus

03930639 JICST ACCESSION NUMBER: 97A0715971 FILE SEGMENT: PreJICST-E
IL-*18* (IFN-.GAMMA. inducer) directly affects in *osteoclastic* precursor cells and suppresses *osteoclastic* differentiation through GM-CSF production.
UDAGAWA NOBUYUKI (1); HORWOOD N J (1); MARTIN T J (1); GILLESPIE M T (1); SUDA TATSUO (2); KURIMOTO MASASHI (3); OKAMURA HARUKI (4); CHAMBERS T J (5)

(1) St.Vincent'sIgakuken; (2) Showa Univ., Sch. of Dent.; (3) Hayashibara Biochem. Lab., Inc.; (4)Hyogo Coll. of Med.; (5) St.George'sIgakuken
Nippon Kotsu Taisha Gakkai Zasshi(Journal of Bone and Mineral Metabolism), 1997, VOL.15,NO.2, PAGE.79
JOURNAL NUMBER: X0157AAW   ISSN NO: 0910-0067
LANGUAGE: Japanese   COUNTRY OF PUBLICATION: Japan
DOCUMENT TYPE: Journal
MEDIA TYPE: Printed Publication

2/7/20   (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09747848 98425700
Interleukin-*18*: perspectives on the newest interleukin.
Gillespie MT; Horwood NJ
St. Vincent's Institute of Medical Research and The University of Melbourne, Department of Medicine, St. Vincent's Hospital, Fitzroy, Vic, Australia. m.gillespie@medicine.unimelb.edu.au
Cytokine Growth Factor Rev (ENGLAND) Jun 1998, 9 (2) p109-16, ISSN 1359-6101 Journal Code: CF7
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
Just over two years ago the newest member of the interleukin family of cytokines, *IL*-*18*, was molecularly cloned. *IL*-*18* was originally identified as a result of its ability to induce interferon gamma production, however with the advent of its cloning and the production of recombinant protein a number of other biological actions have since been identified. Recently the receptor for *IL*-*18* was also characterised. Due to the structural and biological properties shared between *IL*-*18* and IL-1 and their respective receptors, questions relating to *IL*-*18* activities are being answered at a rapid pace. This article addresses the biology of *IL*-*18* in both disease and non-disease states. (48 Refs.)

2/7/21   (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09705258 98380602
Interleukins in the control of *osteoclast* differentiation.
Martin TJ; Romas E; Gillespie MT
St. Vincent's Institute of Medical Research, Victoria, Australia.
Crit Rev Eukaryot Gene Expr (UNITED STATES) 1998, 8 (2) p107-23, ISSN 1045-4403 Journal Code: BEJ
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, ACADEMIC
To maintain homeostasis of bone, the production of osteoblasts and *osteoclasts* is tightly regulated. At the local level, hormones and cytokines control formation of *osteoclasts* from hemopoietic precursors by acting upon osteoblastic-stromal cells and in some cases also upon cells of the immune system. Osteoblasts regulate *osteoclast* formation by providing physical support and cytokines such as M-CSF and IL-11, which promote *osteoclast* differentiation. Osteoblasts are also a source of *IL*-*18*, which limits *osteoclast* formation. The requirement of contact between osteoblasts and hemopoietic cells for successful *osteoclast* formation led to a concept of a membrane-anchored stromal cell molecule that programs *osteoclast* differentiation. This mechanism has been highlighted by the discovery of osteoprotegerin (OPG), a soluble tumor necrosis factor (TNF)

family member that inhibits *osteoclast* formation. The ligand for OPG is a novel transmembrane TNF receptor superfamily member, the *osteoclast* differentiating factor (ODF). The recognition of the osteoprotegerin/osteoprotegerin-ligand axis will lead to new insights into the control of *osteoclast* differentiation by interleukins. (143 Refs.)

2/7/22 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09694363 98119851
Interleukin *18* inhibits *osteoclast* formation via T cell production of granulocyte macrophage colony-stimulating factor.
Horwood NJ; Udagawa N; Elliott J; Grail D; Okamura H; Kurimoto M; Dunn AR ; Martin T; Gillespie MT
St. Vincent's Institute of Medical Research and The University of Melbourne, Department of Medicine, St. Vincent's Hospital, Fitzroy, Victoria 3065, Australia.
J Clin Invest (UNITED STATES) Feb 1 1998, 101 (3) p595-603, ISSN 0021-9738 Journal Code: HS7
Languages: ENGLISH
Document type: JOURNAL ARTICLE
IL-*18* inhibits *osteoclast* (OCL) formation in vitro independent of IFN-gamma production, and this was abolished by the addition of neutralizing antibodies to GM-CSF. We now establish that *IL*-*18* was unable to inhibit OCL formation in cocultures using GM-CSF-deficient mice (GM-CSF -/-). Reciprocal cocultures using either wild-type osteoblasts with GM-CSF -/- spleen cells or GM-CSF -/- osteoblasts with wild-type spleen cells were examined. Wild-type spleen cells were required to elicit a response to *IL*-*18* indicating that cells of splenic origin were the *IL* -*18* target. As T cells comprise a large proportion of the spleen cell population, the role of T cells in *osteoclastogenesis* was examined. Total T cells were removed and repleted in various combinations. Addition of wild-type T cells to a GM-CSF -/- coculture restored *IL*-*18* inhibition of *osteoclastogenesis*. Major subsets of T cells, CD4+ and CD8+, were also individually depleted. Addition of either CD4+ or CD8+ wild-type T cells restored *IL*-*18* action in a GM-CSF -/- background, while *IL*-*18* was ineffective when either CD4+ or CD8+ GM-CSF -/- T cells were added to a wild-type coculture. These results highlight the involvement of T cells in *IL*-*18* -induced OCL inhibition and provide evidence for a new OCL inhibitory pathway whereby *IL*-*18* inhibits OCL formation due to action upon T cells promoting the release of GM-CSF, which in turn acts upon OCL precursors.

2/7/23 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09684560 97228136
Interleukin-*18* (*interferon*-*gamma*-*inducing* *factor*) is produced by osteoblasts and acts via granulocyte/macrophage colony-stimulating factor and not via interferon-gamma to inhibit *osteoclast* formation.
Udagawa N; Horwood NJ; Elliott J; Mackay A; Owens J; Okamura H; Kurimoto M; Chambers TJ; Martin TJ; Gillespie MT
St. Vincent's Institute of Medical Research and The University of Melbourne, Department of Medicine, Victoria, Australia.
J Exp Med (UNITED STATES) Mar 17 1997, 185 (6) p1005-12, ISSN 0022-1007 Journal Code: I2V

Languages: ENGLISH
Document type: JOURNAL ARTICLE

We have established by differential display polymerase chain reaction of mRNA that interleukin (*IL*)-*18* is expressed by osteoblastic stromal cells. The stromal cell populations used for comparison differed in their ability to promote *osteoclast*-like multinucleated cell (OCL) formation. mRNA for *IL*-*18* was found to be expressed in greater abundance in lines that were unable to support OCL formation than in supportive cells. Recombinant *IL*-*18* was found to inhibit OCL formation in cocultures of osteoblasts and hemopoietic cells of spleen or bone marrow origin. *IL*-*18* inhibited OCL formation in the presence of *osteoclastogenic* agents including 1alpha,25-dihydroxyvitamin D3, prostaglandin E2, parathyroid hormone, IL-1, and IL-11. The inhibitory effect of *IL*-*18* was limited to the early phase of the cocultures, which coincides with proliferation of hemopoietic precursors. *IL*-*18* has been reported to induce interferon-gamma (IFN-gamma) and granulocyte/macrophage colony-stimulating factor (GM-CSF) production in T cells, and both agents also inhibit OCL formation in vitro. Neutralizing antibodies to GM-CSF were able to rescue *IL*-*18* inhibition of OCL formation, whereas neutralizing antibodies to IFN-gamma did not. In cocultures with osteoblasts and spleen cells from IFN-gamma receptor type II-deficient mice, *IL*-*18* was found to inhibit OCL formation, indicating that *IL*-*18* acted independently of IFN-gamma production: IFN-gamma had no effect in these cocultures. Additionally, in cocultures in which spleen cells were derived from receptor-deficient mice and osteoblasts were from wild-type mice and vice versa, we identified that the target cells for IFN-gamma inhibition of OCL formation were the hemopoietic cells. The work provides evidence that *IL*-*18* is expressed by osteoblasts and inhibits OCL formation via GM-CSF production and not via IFN-gamma production.

2/7/24 (Item 1 from file: 351)
DIALOG(R)File 351:DERWENT WPI

012032054
WPI Acc No: 98-448964/199839
Use of *interleukin*-*18* to inhibit *osteoclast* formation - in treatment of e.g. hypercalcaemia, *osteoclastoma*, Behcet's syndrome, osteosarcoma, chronic rheumatoid arthritis, deformity ostitis, primary hyperthyroidism and osteoporosis
Patent Assignee: HAYASHIBARA SEIBUTSU KAGAKU (HAYB)
Inventor: GILLESPIE M T; HORWOOD N J; KURIMOTO M; UDAGAWA N
Number of Countries: 025 Number of Patents: 002
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Main IPC	Week
EP 861663	A2	19980902	EP 98301352	A	19980224	A61K-038/20	199839 B
JP 10236974	A	19980908	JP 9755468	A	19970225	A61K-038/00	199846

Priority Applications (No Type Date): JP 9755468 A 19970225
Patent Details:

Patent	Kind	Lan	Pg	Filing Notes	Application	Patent
EP 861663	A2	E	56			

Designated States (Regional): AL AT BE CH DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI

JP 10236974	A		24

Abstract (Basic): EP 861663 A

Use of *interleukin*-*18* (*IL*-*18*) or a functional equivalent for inhibition of *osteoclast* formation is new.

USE - *IL*-*18* is used for treating or preventing *osteoclast* -related diseases (claimed) e.g. hypercalcaemia, *osteoclastoma* Behcet's syndrome, osteosarcoma, arthropathy, chronic rheumatoid arthritis, deformity ostitis, primary hyperthyroidism, osteopaenia and osteoporosis. *IL*-*18* is administered orally, intradermally, subcutaneously, muscularly or intravenously at a dosage of 0.5 mu g to 100 mg (preferably 2 mu g to 10 mg) 2-6 times a day.

Dwg.0/5

Derwent Class: B04; D16

International Patent Class (Main): A61K-038/00; A61K-038/20

International Patent Class (Additional): C07K-014/54; C12N-015/09

2/7/25 (Item 1 from file: 370)

DIALOG(R)File 370:Science

00501040 (USE 9 FOR FULLTEXT)

Activation of *Interferon*- (*gamma*) *Inducing* *Factor* Mediated by Interleukin-1 (beta) Converting Enzyme

Gu, Yong; Kuida, Keisuke; Tsutsui, Hiroko; Ku, George; Hsiao, Kathy; Fleming, Mark A.; Hayashi, Nobuki; Higashino, Kazuya; Okamura, Haruki; Nakanishi, Kenji; Kurimoto, Masashi; Tanimoto, Tadao; Flavell, Richard A. ; Sato, Vicki; Harding, Matthew W.; Livingston, David J.; Su, Michael S.-S.

Y. Gu, G. Ku, K. Hsiao, M. A. Fleming, V. Sato, M. W. Harding, D. J. Livingston, M. S.-S. Su, Vertex Pharmaceuticals Inc., 130 Waverly Street, Cambridge, MA 02139, USA. ; K. Kuida, Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan. ; H. Tsutsui, N. Hayashi, K. Higashino, H. Okamura, K. Nakanishi, Hyogo College of Medicine, 1-1, Mukogawa-cho, Nishinomiya, Japan. ; M. Kurimoto and T. Tanimoto, Fujisaki Institute, Hayashibara Biochemical Laboratories, Hayashibara Company Inc., Okayama, Japan. ; R. A. Flavell, Howard Hughes Medical Institute, Yale University School of Medicine, New Haven, CT 06510, USA.

Science Vol. 275 5297 pp. 206

Publication Date: 1-10-1997 (970110) Publication Year: 1997

Document Type: Journal ISSN: 0036-8075

Language: English

Section Heading: Reports

Word Count: 2474

Abstract: The interleukin-1 (beta) (IL-1 (beta)) converting enzyme (ICE) processes the inactive IL-1 (beta) precursor to the proinflammatory cytokine. ICE was also shown to cleave the precursor of *interferon*- (*gamma*) *inducing* *factor* (*IGIF*) at the authentic processing site with high efficiency, thereby activating *IGIF* and facilitating its export. Lipopolysaccharide-activated ICE-deficient (ICE.sup(-/-)) Kupffer cells synthesized the *IGIF* precursor but failed to process it into the active form. Interferon- (gamma) and *IGIF* were diminished in the sera of ICE.sup(-/-) mice exposed to Propionibacterium acnes and lipopolysaccharide. The lack of multiple proinflammatory cytokines in ICE.sup(-/-) mice may account for their protection from septic shock

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9. A 0.6-kb cDNA encoding full-length murine proIGIF (B6) was ligated into the mammalian expression vector pCDLSRa (B28) . Plasmids for the expression of active human ICE (B11) , TX (B10) , and CMH-1 (B13) lacking the prosequence were as described. Expression plasmid for the active form of CPP32 lacking the prosequence (B12) was constructed similarly in the pCDLSRa vector. Plasmids (3 (mu) g) were transfected into COS cells in 35-nm dishes by the DEAE-dextran method (B11) . Twenty-four hours later, cells were lysed and the lysates were subjected to SDS-PAGE and immunoblotting with an antiserum to *IGIF* (B6) . ;
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14. Expression plasmid for (His).inf(6)-proIGIF was created by introducing Nde I sites at the ends of murine proIGIF cDNA coding sequence (B6) and ligating into Escherichia coli expression vector pET-15B (Novagen). The E. coli strain BL21(DE3) carrying the plasmid was induced with isopropyl-1-thio- (beta) -d-galactopyranoside. (His).inf(6)-proIGIF protein was purified from soluble fractions by Ni-nitrilotriacetic acid-agarose (Qiagen) chromatography according to the manufacturer's instructions. In vitro cleavage reactions by ICE and ICE-like proteases were carried out as in (B29) . Conditions for cleavage by granzyme B were as in (B8) . Cleavage products were analyzed by SDS-PAGE on 16% gels and Coomassie blue staining and were subjected to NH.inf(2)-terminal amino acid sequencing with an ABI automated peptide sequencer. ;
15. [.sup(35)S]methionine-labeled proIGIF [~3000 cpm, prepared by in vitro transcription and translation with the TNT T7 coupled reticulocyte lysate system (Promega) and proIGIF cDNA in pSP73 vector as template] was incubated in reaction mixtures of 60 (mu) l containing 0.1 to 1 nM recombinant ICE and 190 nM to 12 (mu) M unlabeled proIGIF for 8 to 10 min at 37.Deg.C. Cleavage product concentrations were determined by SDS-PAGE and PhosphorImager analysis. The kinetic parameters were calculated by nonlinear regression fitting of the rate versus concentration data to the Michaelis-Menten equation by means of the program Enzfitter (Biosoft). ;
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17. The T.inf(H)1 A. E7 cells (B30) (1.3 x 10.sup(5) cells in 0.15 ml) or nonadherent splenic T cells (8 x 10.sup(5) cells) in 96-well plates were treated with *IGIF* or conditioned medium for 18 to 20 hours, and the culture supernatants were assayed for IFN- (gamma) by ELISA (Endogen, Cambridge, MA). ;
18. COS cells (3.5 x 10.sup(5) cells in a 35-mm dish) were labeled for 7 hours with 1 ml of methionine-free Dulbecco's modified Eagle's medium (DMEM) containing 2.5% normal DMEM, 1% dialyzed fetal bovine serum (FBS), and [.sup(35)S]methionine (300 (mu) Ci/ml; [.sup(35)S]Express Protein Labeling Mix, New England Nuclear). Cell lysates [prepared in 20 mM Hepes (pH 7.2), 150 mM NaCl, 0.1% Triton X-100, 5 mM N-ethylmaleimide, 1 mM phenylmethylsulfonyl fluoride, and leupeptin (2.5 (mu) g/ml)] or conditioned medium were immunoprecipitated with the antiserum to *IGIF* (B6) . ;

19. COS cells (3.5 x 10.sup(5) cells in a 35-mm dish) were transfected and grown in 1 ml of medium for 18 hours. Medium was harvested and used at 1:10 final dilution in the IFN- (gamma) induction assay (B17) ; COS cell pellets from the same transfection were lysed in 100 (mu) l of 20 mM Hepes (pH 7.0) by three cycles of freezing and thawing. Lysates were cleared by centrifugation and were used at 1:10 dilution in the assay. On the basis of our analysis that 10% mature *IGIF* was exported out of the cells, we estimated that the mature *IGIF* concentration in lysates is ~90 times that of the conditioned medium. ;
20. Wild-type or ICE-deficient mice were injected intraperitoneally with 1 mg of heat-killed P. acnes (B5) . Kupffer cells were prepared 7 days later (B31) , except that nycodenz gradient was used instead of metrizamide. For each experiment, Kupffer cells (1 x 10.sup(6) cells per milliliter) from two or three animals were pooled and cultured in RPMI 1640 supplemented with 10% FBS and LPS (1 (mu) g/ml; Difco, E. coli strain 055:B5). Cell lysates and conditioned media were prepared 3 hours later. *IGIF* was determined by ELISA with protein G-purified rabbit polyclonal antibody to murine *IGIF* (B6) . Metabolic labeling and immunoprecipitation experiments were carried out as for COS cells (B18) except that methionine-free RPMI 1640 was used in place of DMEM. To prepare conditioned medium of LPS-stimulated adherent splenocytes, we cultured total splenic cells (6 x 10.sup(7) cells in 1 ml) from wild-type or ICE.sup(-/-) mice for 1 hour. Adherent cells were then stimulated with LPS (50 ng/ml) for 5 hours. Conditioned media were harvested and used at 1:4 dilution in the IFN- (gamma) assay (B17) in the presence or absence of anti-*IGIF* (25 (mu) g/ml) (B6) . ;
21. Wild-type or ICE-deficient mice were primed with P. acnes (B20) . Seven days later, mice were exposed to LPS (1 (mu) g, intravenously). In some experiments, recombinant mature *IGIF* (1 (mu) g) or protein G-purified anti-*IGIF* (250 (mu) g) was coinjected with LPS; sera were collected 3 hours after LPS exposure. ;
22. Reduced IFN- (gamma) was also observed in Listeria-infected (N. M. Tsuji et al., in preparation) and LPS-exposed (G. Ku et al., in preparation) ICE.sup(-/-) mice. ;
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32. We thank T. Fox and W. Chen for ICE and TX protein; A. Diu, C. Faucheu, and J.-L. Lalanne for TX cDNA; M. Rincon for A. E7 cells; J. Lippke for CPP32 and CMH-1 cDNA; B. O'Hare for oligonucleotide synthesis and DNA sequencing; T. Faust for ELISA; A. Heiser for animal surgery; and J. Boger for critical reading and discussion of the manuscript. R.A.F. is an HHMI Investigator.

2/7/26 (Item 1 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

09195096
ISSN: 0021-9738
JOURNAL: JOURNAL OF CLINICAL INVESTIGATION
(TABLE OF CONTENTS RECORD)
(The Complete Table of Contents now Available in Format 19)

2/7/27 (Item 2 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

09195081 GENUINE ARTICLE#: YW195 NUMBER OF REFERENCES: 25
TITLE: *Interleukin* *18* inhibits *osteoclast* formation via T cell production of granulocyte macrophage colony-stimulating factor
AUTHOR(S): Horwood NJ; Udagawa N; Elliott J; Grail D; Okamura H; Kurimoto M ; Dunn AR; Martin TJ; Gillespie MT (REPRINT)
CORPORATE SOURCE: ST VINCENTS INST MED RES,41 VICTORIA PARADE/FITZROY/VIC 3065/AUSTRALIA/ (REPRINT); ST VINCENTS INST MED RES,/FITZROY/VIC 3065/AUSTRALIA/; UNIV MELBOURNE,ST VINCENTS HOSP, DEPT MED/FITZROY/VIC 3065/AUSTRALIA/; SHOWA UNIV,SCH DENT, DEPT BIOCHEM/TOKYO 142//JAPAN/; LUDWIG INST CANC RES,/PARKVILLE/VIC 3052/AUSTRALIA/; HYOGO MED UNIV,DEPT IMMUNOL & MED ZOOL/NISHINOMIYA/HYOGO 663/JAPAN/; HAYASHIBARA BIOCHEM LABS INC,FUJISAKI INST/OKAYAMA 702//JAPAN/
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LANGUAGE: English DOCUMENT TYPE: ARTICLE
ABSTRACT: *IL*-*18* inhibits *osteoclast* (OCL) formation in vitro independent of IFN-gamma production, and this was abolished by the addition of neutralizing antibodies to GM-CSF, We now establish that *IL*-*18* was unable to inhibit OCL formation in cocultures using GM-CSF-deficient mice (GM-CSF -/-). Reciprocal cocultures using either wild-type osteoblasts with GM-CSF -/- spleen cells or GM-CSF -/- osteoblasts with wild-type spleen cells were examined. Wild-type spleen cells were required to elicit a response to *IL*-*18* indicating that cells of splenic origin were the *IL*-*18* target. As T cells comprise a large proportion of the spleen cell population, the role of T cells in *osteoclastogenesis* was examined. Total T cells were removed and repleted in various combinations, Addition of wild-type T cells to a GM-CSF -/- coculture restored *IL*-*18* inhibition of *osteoclastogenesis*, Major subsets of T cells, CD4(+) and CD8(+), were also individually depleted, Addition of either CD4(+) or CD8(+) wildtype T cells restored *IL*-*18* action in a GM-CSF -/- background, while *IL*-*18* was ineffective when either CD4(+) or CD8(+) GM-CSF -/- T cells were added to a wild-type coculture. These results highlight the involvement of T cells in *IL*-*18*-induced OCL inhibition and provide evidence for a new OCL inhibitory pathway whereby *IL*-*18* inhibits OCL formation due to action upon T cells promoting the release of GM-CSF, which in turn acts upon OCL precursors.

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JOURNAL: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS
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08296587 GENUINE ARTICLE#: WP404 NUMBER OF REFERENCES: 39
TITLE: *Interleukin*-*18* (*interferon*-*gamma*-*inducing* *factor*) is produced by osteoblasts and acts via granulocyte/macrophage colony-stimulating factor and not via interferon-gamma to inhibit *osteoclast* formation
AUTHOR(S): Udagawa N; Horwood NJ; Elliott J; Mackay A; Owens J; Okamura H; Kurimoto M; Chambers TJ; Martin TJ; Gillespie MT (REPRINT)
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LANGUAGE: English DOCUMENT TYPE: ARTICLE
ABSTRACT: We have established by differential display polymerase chain reaction of mRNA that interleukin (*IL*)-*18* is expressed by osteoblastic stromal cells. The stromal cell populations used for comparison differed in their ability to promote *osteoclast*-like multinucleated cell (OCL) formation. mRNA for *IL*-*18* was found to be expressed in greater abundance in lines that were unable to support OCL formation than in supportive cells. Recombinant *IL*-*18* was found to inhibit OCL formation in cocultures of osteoblasts and hemopoietic cells of spleen or bone marrow origin. *IL*-*18* inhibited OCL formation in the presence of *osteoclastogenic* agents including 1 alpha,25-dihydroxyvitamin D-3, prostaglandin E(2), parathyroid hormone, IL-1, and IL-11. The inhibitory effect of *IL*-*18* was limited to the early phase of the cocultures, which coincides with proliferation of hemopoietic precursors. *IL*-*18* has been reported to induce interferon-gamma (IFN-gamma) and granulocyte/macrophage colony-stimulating factor (GM-CSF) production in T cells, and both agents also inhibit OCL formation in vitro. Neutralizing antibodies to

GM-CSF were able to rescue *IL*-*18* inhibition of OCL formation, whereas neutralizing antibodies to IFN-gamma did not. In cocultures with osteoblasts and spleen cells from IFN-gamma receptor type II-deficient mice, *IL*-*18* was found to inhibit OCL formation, indicating that *IL*-*18* acted independently of IFN-gamma production: IFN-gamma had no effect in these cocultures. Additionally, in cocultures in which spleen cells were derived from receptor-deficient mice and osteoblasts were from wild-type mice and vice versa, we identified that the target cells for IFN-gamma inhibition of OCL formation were the hemopoietic cells. The work provides evidence that *IL*-*18* is expressed by osteoblasts and inhibits OCL formation via GM-CSF production and not via IFN-gamma production.

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